Innovations in colorectal cancer surgery

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Innovations in colorectal cancer surgery

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geboren te Amsterdam

promotor: prof.dr. H.J. Bonjer
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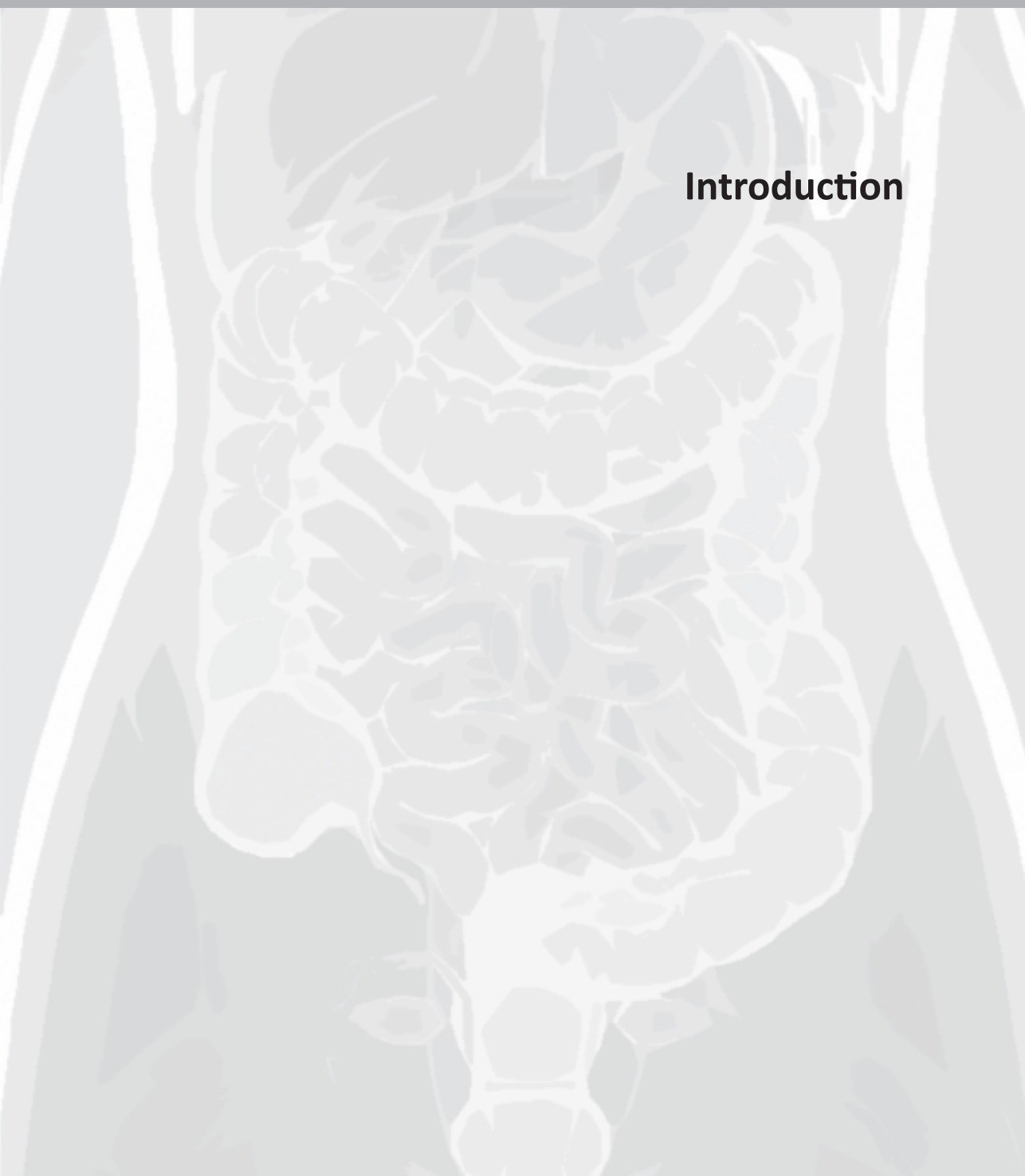
CHAPTER 1

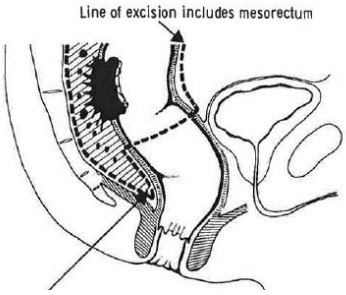
Introduction



Colorectal cancer afflicts approximately 1,361,000 patients every year and accounts for 694,000 deaths per year worldwide. In females it is the second most common form of cancer, after breast cancer, and in males it is the third most common form after prostate and lung cancer. One third of all colorectal cancers is located in the rectum.[1-4]

Two centuries ago rectal cancer was an incurable disease with mortality rates of 100% and recurrence at the surgical site (local recurrence) in 4 out of 5 patients.[5] In 1908 Miles published the concept of cylindrical lymphatic spread of cancer cells. Therefore, he recommended a more extensive surgical resection of the anus and rectum, including the lymph nodes, in order to prevent recurrence. This technique was called 'abdominoperineal resection' (APR) and is considered the basis for modern rectal cancer surgery.[6] However, because this procedure consisted of blunt dissection of the rectum, high rates of irradical resections were reported, which predispose to local recurrence. Despite improvement in survival and recurrence rates, less than half a century ago rectal cancer still had a poor prognosis with local recurrence rates of up to 40% and 5-year survival rates after surgery of less than 50%.[7]

In 1982 one of the most important developments in rectal cancer treatment was published by Heald. He introduced the concept of radial spread of tumor cells and therefore advocated total mesorectal excision (TME), in which sharp excision of the rectum, including the complete fatty envelope surrounding the rectum (mesorectum), is performed.



This more extensive excision resulted in significant decrease of local recurrence rates to 3.7% and improved survival rates to 87% at 5-years after surgery.[8,9] Nowadays, the most potential curative treatment for patients with rectal cancer is TME surgery combined with preoperative (chemo)radiotherapy.

Since the 1980's there has been more focus on reducing surgical trauma. It was hypothesized that this would not only improve postoperative recovery, but also result in less tumor recur-

rence and therefore improved survival.[10,11] The conventional rectal resection is performed through one abdominal incision, resulting in a large scar. In the early 1990's laparoscopic (keyhole) surgery was introduced. Instead of operating through one large incision, several small abdominal incisions are made and surgery is performed with smaller instruments and a laparoscope, producing a magnified image of the operating field.

At first, it was shown that this minimally invasive technique was safe and resulted in less blood loss, less pain and enhanced recovery after resection of the gallbladder and appendix, followed by laparoscopic surgery for colon cancer. However, there were concerns if the procedure would not compromise the quality of the resection. Several randomized trials comparing open and laparoscopic surgery for colon cancer were conducted, including the Dutch COlon cancer Laparoscopic or Open Resection (COLOR) trial, reporting similar pathology results, as well as similar recurrence and survival rates.[12-17] A study by Lacy et al. even showed improved disease-free survival in patients with stage III disease.[16]

Subsequently, laparoscopic surgery was performed in patients with rectal cancer. However, rectal cancer surgery is considered technically more challenging than colon surgery, mainly because of the limited workspace in the lower pelvis and fibrosis of the tissue as a result of neoadjuvant radiotherapy. As for colon cancer, laparoscopic surgery resulted in short-term benefits for patients with rectal cancer.[14,18]

Because evidence was lacking from large, randomized clinical trials indicating that survival after laparoscopic resection of rectal cancer is not inferior to open surgery, the COLOR II trial was initiated, including more than 1000 patients.[19] The primary endpoint, local recurrence 3 years after index surgery, was similar at 5% in both treatment groups. Disease-free and overall survival rates were similar as well. Comparable to the colon cancer study by Lacy, in patients with stage III rectal cancer better disease-free survival was observed in patients after laparoscopic surgery.[20] These observations may confirm the experimental findings that less surgical trauma associated with the use of laparoscopic techniques reduces tumor recurrence.[10,11] In a study involving patients undergoing laparoscopic and open colonic resection, laparoscopic surgery was followed by attenuated stress responses and improved preservation of immune function.[21]

Although laparoscopic rectal cancer surgery has gained popularity over the past decade, especially mid and low rectal cancers are technically demanding due to the requirement of a complete mesorectal excision down to the pelvic floor. Total complication rates of laparo-

scopic surgery in the larger randomized trials have been reported up to 57%.[14,19,22-24] As incomplete resection of the tumor predisposes to the development of local recurrence, the involvement of the circumferential resection margin with tumor cells is one the main pathology parameters. In recent trials involvement of this margin has been reported in 2.9% to 12.1% of the patients who underwent laparoscopic resection of rectal cancer. However, there is no direct correlation between circumferential resection margin involvement and local recurrence. In the first multicenter randomized trial comparing laparoscopic and open surgery for rectal cancer (the Conventional versus Laparoscopic-Assisted Surgery In Colorectal Cancer (CLASICC) trial), a higher rate of involved circumferential resection margin was found in patients after laparoscopic resection of rectal cancer (12%) compared to open resection (6%). However, this difference did not translate into higher local recurrence rates in patients after laparoscopic surgery 3 years after surgery.[25] One of the other problems in rectal cancer surgery is the proportion of APRs. Several large trials and two national surveys reported APR rates up to 32%.[14,19,24-27] APR shows high morbidity, mostly presacral abscess and infection of the perineal wound. Furthermore, the high colostomy rate could lead to a reduced quality of life. On the contrary, bowel continuity restoration can result in problems of fecal incontinence, urgency and frequent bowel movements, called low anterior resection syndrome (LARS).[28] A report on sexual and urinary dysfunction showed similar rates of changes in genitourinary function in patients after laparoscopic surgery compared to open surgery. Micturition symptoms gradually improved to preoperative levels at 6 months postoperatively. However, in both groups in some male sexual problems persisted.[29] Especially in patients with mid and low rectal cancer there is potential for improvement with respect to reduction in morbidity, incomplete resections, the proportion of permanent colostomies and functional and genitourinary outcome.

In 2010 the transanal approach was introduced by the group of Lacy.[30] In transanal total mesorectal excision (TaTME) the tumor is approached through the anus and direct endoscopic visualization of the tumor facilitates exact dissection of the distal resection margin, and presacral and perirectal planes. Furthermore, because the tumor is approached from below, use of a stapler to transect the rectum can be avoided. Other potential benefits of TaTME are less anastomotic leakages, better quality of resection resulting in less involved circumferential margins, more sphincter saving procedures and improved sphincter function. TaTME can be particularly advantageous in case of the narrow male pelvis and distally located tumors.

A significant problem when implementing a new surgical technique is the learning curve of surgeons and team. Because the TaTME is performed in a bottom-up fashion, lack of anatomical landmarks can be a pitfall when performing the procedure. In order to avoid unwanted

negative outcome such as damage of urethra and prostate and rectal perforation, quality assurance and controlled safe implementation seems essential. Several TaTME expert centers across Europe and the US provide training workshops and facilitate proctoring of the technique. The TaTME has high potential, however extensive evaluation in a well-designed multicenter randomized trial is needed to come to unequivocal conclusions.

The research questions addressed in this thesis are:

1. Is laparoscopic surgery for colon cancer as safe as open surgery at 10 years follow-up? After laparoscopic resection of colon cancer showed short-term benefits and was proven to be safe up to 5 years after surgery, it was unclear whether the outcomes reported would remain present at 10 years.
2. Is laparoscopic surgery for rectal cancer noninferior to open surgery with primary endpoint local recurrence rate? What are the benefits of laparoscopic surgery?
3. Is transanal surgery for rectal cancer noninferior to laparoscopic surgery with primary endpoint local recurrence rate? What are the benefits of transanal surgery?

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CHAPTER 2

State of the art in rectal cancer surgery: historical overview and new perspectives after the COLOR II trial

Deijen CL, van den Broek JJ, Poelman MM, Schreurs WH, Tuynman JB, Sietses C, Bonjer HJ. On behalf of the COLOR (COlon cancer Laparoscopic or Open Resection) Study Group.

Cir Esp. 2016 Jan;94(1):1-3.

Rectal cancer treatment has significantly changed during the past two centuries. Development of new surgical techniques and introduction of (neo) adjuvant therapies have contributed to the improved prognosis of rectal cancer and reduced morbidity rates. The first technically successful excision of rectal cancer was performed by LisFranc in 1826. It was a primitive procedure without anesthesia or hemostasis and the patient did not survive.[1] In those days operative mortality rates of 20% and local recurrence rates of 80% were reported.[2] In 1908 Miles published the concept of cylindrical lymphatic spread of cancer cells. He recommended more extensive mesenteric lymphadenectomy combined with resection of the anus and rectum in order to prevent recurrence.[3] With the introduction of this radical 'abdominoperineal resection' (APR), Miles established the basis for modern rectal cancer surgery. Because the APR resulted in creation of a permanent colostomy, considered a great disadvantage for the patients, halfway through the twentieth century the focus shifted toward sphincter-sparing procedures and the 'anterior resection' (AR) became the standard treatment for mid and high rectal cancer. Subsequently, in the 1970s the restoration of bowel continuity after AR was introduced.[4] In order to decrease anastomotic leakage rates and pelvic sepsis, adjustments were made such as creation of a colonic J-pouch anastomosis or diverting ileostomy. However, both the APR and AR included blunt dissection of the rectum along the presacral fascia with a cone-wise development of the most distal part of the rectum. This blunt technique resulted in high rates of involved circumferential resection margins (CRMs), which predisposes to local recurrence, and local recurrence rates up to 40% were reported.[5] In 1982 Heald et al. introduced the technique of total mesorectal excision (TME), in which sharp excision of the complete mesorectum en bloc with the tumor to the level of the levator muscles was performed following the anatomical planes. This more extensive excision resulted in significant decrease of involved CRMs and decreased local recurrence rates to 3.7% at 5-years postoperatively.[6] In the 1980s it was hypothesized that less surgical trauma would not only improve postoperative recovery, moreover it would result in less tumor recurrence and therefore improved survival.[7] Following laparoscopic resection of the gallbladder and appendix, laparoscopic colorectal surgery was first described by Jacobs et al.[8] For colon cancer, evidence was obtained that laparoscopic surgery was safe, causing less postoperative pain, shorter hospital stay, and resulting in comparable survival rates compared with open colectomy.[9,10] However, rectal cancer surgery is considered technically more challenging than colon surgery, mainly because of the limited workspace in the lower pelvis and fibrosis of the tissue as a result of neoadjuvant radiotherapy.

Recent studies showed improved short-term outcomes as well as comparable oncological outcomes after laparoscopic TME for rectal cancer compared with open TME.[11,12] However, these studies included small numbers of patients. The largest randomized trial comparing laparoscopic and traditional open resection for rectal cancer is the COLOR II trial. It was undertaken in 30 hospitals in 8 countries and 1044 patients were included. Short-term outcomes showed less blood loss, less pain and shorter hospital stay after laparoscopic resection with comparable quality of the resected specimen as in open surgery.[13] Recently, the COLOR II study group published their long-term outcomes and reported that laparoscopic surgery for rectal cancer resulted in similar rates of local recurrence and disease-free and overall survival compared with open surgery.[14] However, patients were included over a period of 6 years (2004-2010) and analysis of the long-term endpoints (including the primary endpoint) could at the earliest be performed 3 years after the inclusion of the last patient. The interval between commencement of randomized clinical trials accruing high numbers of patients and reporting long-term outcomes lasts in most instances approximately a decade. Within that time frame, management protocols in health care frequently change and are implemented in the care of those patients involved in the clinical trial rendering interpretation of some outcomes more complex. Furthermore, a major challenge in surgical cancer clinical trials is lack of consistency in surgical quality. Even though centers had to submit five unedited recordings of laparoscopic TME before entering the COLOR II trial, learning curve evaluation and quality assessment during the trial was not performed.

Although laparoscopic rectal cancer surgery has gained popularity over the past decade, there is potential for improvement with respect to reduction in incomplete resections, morbidity, and sphincter-saving procedures. In distal rectal tumors, mobilization of the rectum below the tumor can be difficult, due to the coning of the pelvis, and leading to unradical resection. Involvement of the CRM is reported in 3%-16% of the patients after rectal carcinoma resection.[11-13] In order to achieve clear CRMs, the surgeon might choose to perform an APR, which is performed in approximately 25%-30% of rectal resections.[11,13] Both un-radical resection and APR cause higher morbidity, which is reported up to 40%.[13] Because of the limited workspace in the pelvis, rectal resection with TME is probably more suitable for laparoscopic than for open resection. But especially in obese male patients and patients with bulky tumors resection of lower rectal cancers remains difficult.

The transanal TME (TaTME) has been introduced in 2009 by Lacy et al. In TaTME, the tumor is approached through the anus, giving better visualization and facilitating the mobilization of the distal rectum including its mesorectum.[15] Therefore, even in low rectal cancer a coloanal anastomosis can be created and the resection can be more radical.

Currently, several cohort series have been published showing rates of involved CRMs of 0%-5.4% and comparable short-term outcomes as traditional laparoscopic rectal cancer resection.[16-19] The transanal laparoscopic 'bottom-up' TME appears a promising technique requiring evaluation in a randomized clinical trial. To the best of our knowledge, no randomized trials have been started. The COLOR II study group is preparing a proposal for a large international randomized trial comparing transanal TME and laparoscopic TME for mid and low rectal cancer. The trial will be named COLOR III trial and has an expected start in 2015. International collaboration is mandatory to reduce completion times of large randomized trials and is essential for the COLOR III trial. Furthermore, this study aims at addressing the limitation of evaluation of the surgical quality by applying a robust surgical quality assurance protocol prior to the start and throughout the clinical trial to ensure consistency and validity.

What if the TaTME proves to be better than laparoscopic surgery for rectal cancer? Will there be no place for the 'traditional' laparoscopic resection in the treatment of rectal cancer? As mentioned before, TaTME provides the most benefit in distal rectal tumors. For proximal rectal tumors, the laparoscopic resection is still the gold standard. However, laparoscopic rectal resection remains technically challenging and should only be performed in centers with experienced laparoscopic colorectal surgeons after sufficient training.

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PART I

THE PAST & PRESENT: COLOR & COLOR II

CHAPTER 3

Ten-year outcomes of a randomised trial of laparoscopic versus open surgery for colon cancer

Deijen CL, Vasmel JE, de Lange-de Klerk ESM, Cuesta MA, Coene PPLO, Lange JF, Meijerink WJHJ, Jakimowicz JJ, Jeekel J, Kazemier G, Janssen IMC, Påhlman L†, Haglind E, Bonjer HJ; COLOR Study Group.

Surg Endosc. 2017 Jun;31(6):2607-2615.

Abstract

Background Laparoscopic surgery for colon cancer is associated with improved recovery and similar cancer outcomes at 3 and 5 years in comparison to open surgery. However, long-term survival rates have rarely been reported. Here, we present survival and recurrence rates of the Dutch patients included in the COLOR (COlon cancer Laparoscopic or Open Resection) trial at 10-year follow-up.

Methods Between March 1997 and March 2003 patients with non-metastatic colon cancer were recruited by 29 hospitals in eight countries, and randomised to either laparoscopic or open surgery. Main inclusion criterion for the COLOR trial was solitary adenocarcinoma of the left or right colon. The primary outcome was disease-free survival at 3 years, secondary outcomes included overall survival and recurrence. The 10-year follow-up data of all Dutch patients were collected. Analysis was by intention-to-treat. The trial was registered at ClinicalTrials.gov (NCT00387842).

Results In total, 1248 patients were randomised, of which 329 were Dutch. Fifty-eight Dutch patients were excluded and 15 were lost to follow-up, leaving 256 patients for 10-year analysis. Median follow-up was 112 months. Disease-free survival rates were 45.2% in the laparoscopic group and 43.2% in the open group (difference 2.0%; 95% confidence interval (CI), -10.3 to 14.3; p=0.96). Overall survival rates were 48.4% and 46.7% respectively (difference 1.7%; 95% CI, -10.6 to 14.0; p=0.83). Stage specific analysis revealed similar survival rates for both groups. Sixty-two patients were diagnosed with recurrent disease, accounting for 29.4% in the laparoscopic group and 28.2% in the open group (difference 1.2%; 95% CI, -11.1 to 13.5; p=0.73). Seven patients had port- or wound-site recurrences (laparoscopic n=3 versus open n=4).

Conclusions Laparoscopic surgery for non-metastatic colon cancer is associated with similar rates of disease-free survival, overall survival, and recurrences as open surgery at 10-year follow-up.

Introduction

Laparoscopic surgery for colon cancer has proven to result in short-term benefits compared to open surgery, such as reduced blood loss, less postoperative pain, and shorter length of hospital stay.[1-3] However, there are few studies on long-term outcomes of laparoscopic and open surgery for colon cancer.[4-7] This is remarkable, as malignancy of the colon and rectum is the third most common malignancy worldwide, accounting for approximately 1 361 000 new patients and 694 000 deaths every year.[8]

Early detection of recurrent colon cancer is important because prompt management of these recurrences is associated with improved survival.[9] Current colon cancer guidelines advocate follow-up up to 5 years after surgery.[9,10] Nevertheless, knowledge of the course of disease beyond the period of 5 years is limited. Therefore, it remains unclear whether limiting follow-up to 5 years postoperatively is sufficient.

The COLOR (COlon cancer Laparoscopic or Open Resection) trial was designed as an international multicentre randomised trial to demonstrate non-inferiority of laparoscopic surgery for colon cancer compared with the conventional open resection.[11] Previously, 3- and 5-year results have been published and similar survival outcomes for both groups were reported.[12] Here, we present the long-term outcomes of Dutch patients included in the COLOR trial at 10-years follow-up.

Materials and methods

Study design

The COLOR trial is a randomised, non-inferiority, open-label trial. Between March 1997 and March 2003, patients were recruited by 29 hospitals in eight countries. The trial was approved by the ethics committee of each participating hospital. Because 10-year follow-up was not included in the initial COLOR trial protocol, the study had to be re-opened in all participating countries separately. The Netherlands is a relative small country and its geography made it possible to accurately check all medical records and collect all data. Therefore, only data of Dutch patients was used for this study. The ethical committee of VUmc approved 10-year follow-up of all Dutch patients. This trial is registered at ClinicalTrials.gov, number NCT00387842.

Participants

The main criterion for inclusion in the COLOR trial was non-metastatic solitary adenocarcinoma of the caecum, ascending colon, descending colon, or sigmoid colon above the peritoneal deflection. Tumours of the transverse colon or splenic flexure were not included in this study because laparoscopic surgery of these tumours was considered technically more challenging and prone to conversion to open surgery. Diagnosis was to be made by barium enema radiography or colonoscopy. A biopsy was required in polyps, not in macroscopically evident adenocarcinomas. Metastatic disease was excluded by radiological imaging of the chest and liver. Exclusion criteria were: Body Mass Index > 30, distant metastases, multiple primary colon tumours, invasion of adjacent structures, signs of obstruction, previous ipsilateral surgery of the colon, history of malignant disease (with the exception of curative treatment for basal cell carcinoma of the skin or in-situ carcinoma of the cervix), and absolute contraindication for general anesthesia or pneumoperitoneum. All patients gave written informed consent.

Randomisation and masking

Eligible patients were assigned to either laparoscopic resection or open resection at random in a 1:1 ratio and stratified according to participating centre and type of resection. Randomisation was performed by the trial coordinator (RV, who was succeeded by EK) at Erasmus University Medical Center, Rotterdam, Netherlands, and allocation was performed by telephone or fax. Neither patients nor care-givers were blinded to the result of randomisation.

Procedures

Patients in both groups had the same extent of resections: in right hemicolectomy a resection of the caecum, ascending colon and hepatic flexure, in left hemicolectomy a resection with

a margin of at least 5cm below and 5cm above the lesion, in sigmoidectomy a resection of the sigmoid of at least 5cm below and 5cm above the lesion. Pre- and postoperative care and adjuvant treatment were applied according to local protocols.

Follow-up for both groups was required at least once a year during the first 5 postoperative years and included colon, liver, and thorax imaging studies at 3-year follow-up. After 5 years, further follow-up was at the surgeon's discretion. Participating centres treated detected recurrences according to local protocols, including resection and chemotherapy. Surgical teams had performed at least 20 laparoscopically assisted colectomies and had to submit an unedited videotape of a laparoscopically assisted colectomy to assess safety of surgical techniques before entering the trial. Patients in the laparoscopic group could be converted preoperatively to an open resection if there was malfunctioning equipment or if no surgeon with laparoscopic skills was available. All converted patients, i.e. preoperative and intraoperative, remained in the laparoscopic group for analysis based on intention-to-treat principle.

Outcomes

The primary outcome was disease-free survival at 3 years, which has been reported earlier.[12] Secondary outcomes included overall survival and pattern of recurrence. Recurrences were defined as local or distant. Furthermore, we defined local recurrence as recurrence at the surgical site or port- or wound-site and distant recurrence as all other recurrences. When no clinical signs of recurrence were present at 10-year follow-up, further imaging was not done and the patient was considered as not having recurrent disease. For 10-year follow-up results, data of all Dutch patients was collected. The Hospital Information System was used to collect details at 10 years after index surgery and when no information was available, the general practitioner of the patient was consulted. If information about survival of the patients was missing, the Municipal Personal Records Database was checked.

Statistical analyses

Analyses were performed according to the intention-to-treat principle. Baseline characteristics were compared by using Student's t-test or a Mann-Whitney U test for numerical variables and a Chi-square test or an exact test where necessary. The Kaplan-Meier method was used to calculate the median follow-up period[13] and 10-year disease-free survival, overall survival and recurrence rates. Survival was calculated as time from surgery to last date of follow-up or date of death. IBM SPSS version 22 was used for statistical analyses.

Results

Patients

In total 1248 patients were randomly assigned to either laparoscopic resection or conventional open resection, of which the six participating Dutch centres recruited 329. Of the Dutch patients, 58 were excluded for various reasons (Figure 1). The first patient inclusion in the Netherlands was at March 21, 1997, and the last at March 10, 2003. In November 2014 collecting of 10-year follow-up data was started. In the laparoscopic and open group six and nine patients respectively had been lost to follow-up, leaving 256 patients for 10-year analysis. Of those, 125 patients were assigned to be operated laparoscopically and 131 patients to be operated through an open procedure (Figure 1). The median follow-up of all patients was 112 months in the laparoscopic group (range 0.03 to 198.92) and 111 months in the open group (range 0.10 to 194.89) (p=0.83). Median follow-up of survivors was 156 months in the laparoscopic group (range 117.97 to 198.92) and 150 months in the open group (range 105.11 to 194.13).

Baseline characteristics showed no significant differences between the two groups (Table 1). Operative and pathological data showed no differences except for length of operative procedure, which was longer in the laparoscopic group (140 minutes versus 95 minutes, p<0.001) and blood loss, which was less in the laparoscopic group (113 mL versus 200 mL, p=0.02). Distribution of disease stage and size of tumour was similar in both groups (Table 2).

Conversion

Of 125 patients who were assigned to undergo a laparoscopic procedure, conversion to open surgery was performed in 40 patients (32%). In six patients the decision for conversion was made preoperatively (poor cardiac condition (n=3), randomisation error (n=1), extensive T4 tumour (n=1) and unknown (n=1)). In 34 patients (27%) conversion was performed during the operation, reasons were fixation of the tumour (n=10), adhesions (n=3), the tumour could not be identified (n=8), macroscopic metastases were found (n=2), other reasons (n=10), and in one patient the reason was unknown.

Disease-free survival

The disease-free survival rate at 10 years postoperatively was 45.2% in the laparoscopic group and 43.2% in the open group (difference 2.0%; 95% confidence interval (CI), -10.3 to 14.3); p=0.96). In patients with stage I colon cancer, disease-free survival rates were 54.8% and 45.9% for the laparoscopic and open group respectively (difference 8.9%; 95% CI, -16.2 to 34.0; p=0.52). In patients with stage II disease these rates were 48.1% and 35.7% (difference 12.4%;

95% CI, -5.9 to 30.7; p=0.22) and in patients with stage III disease 34.2% in the laparoscopic group and 52.5% in the open group (difference -18.3%; 95% CI, -39.9 to 3.3; p=0.09) (Figure 2).

Figure 1. Trial profile

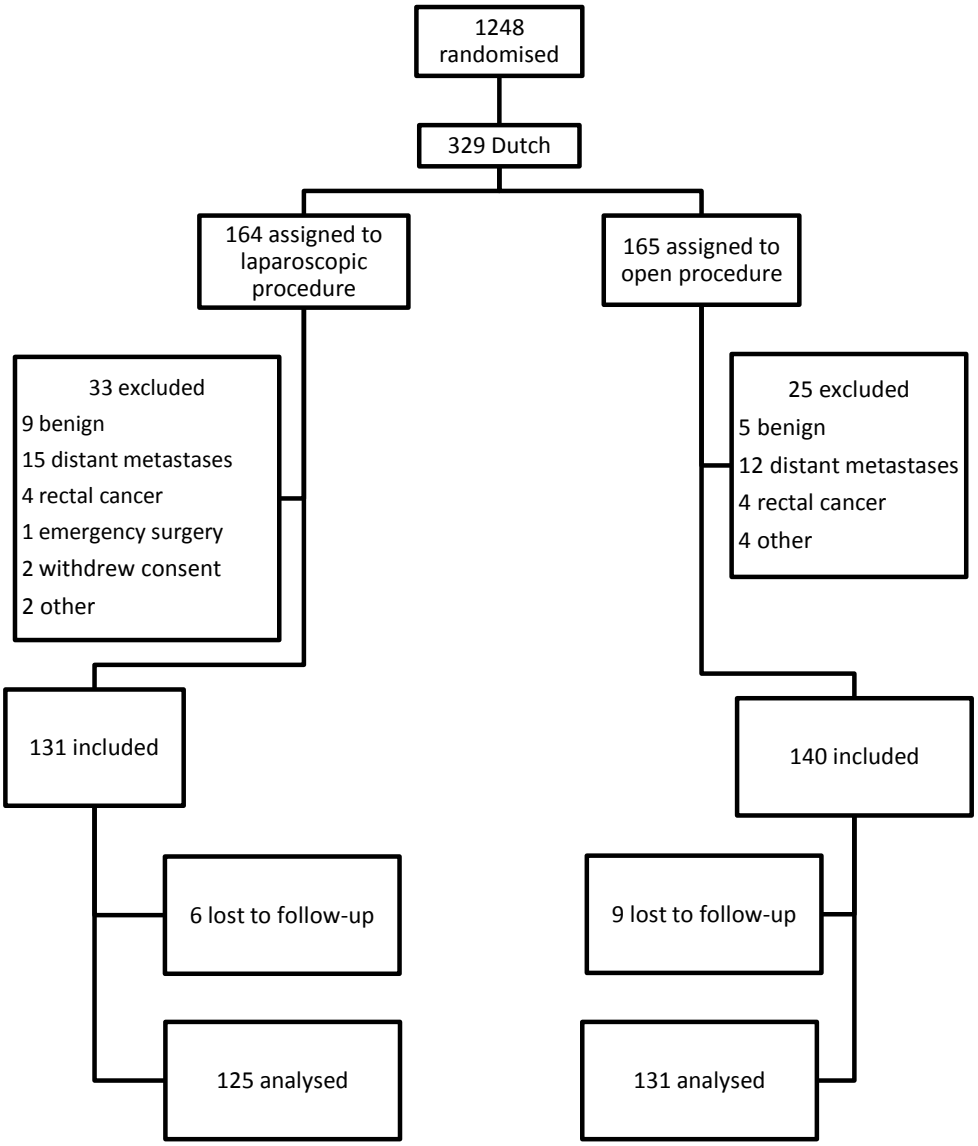
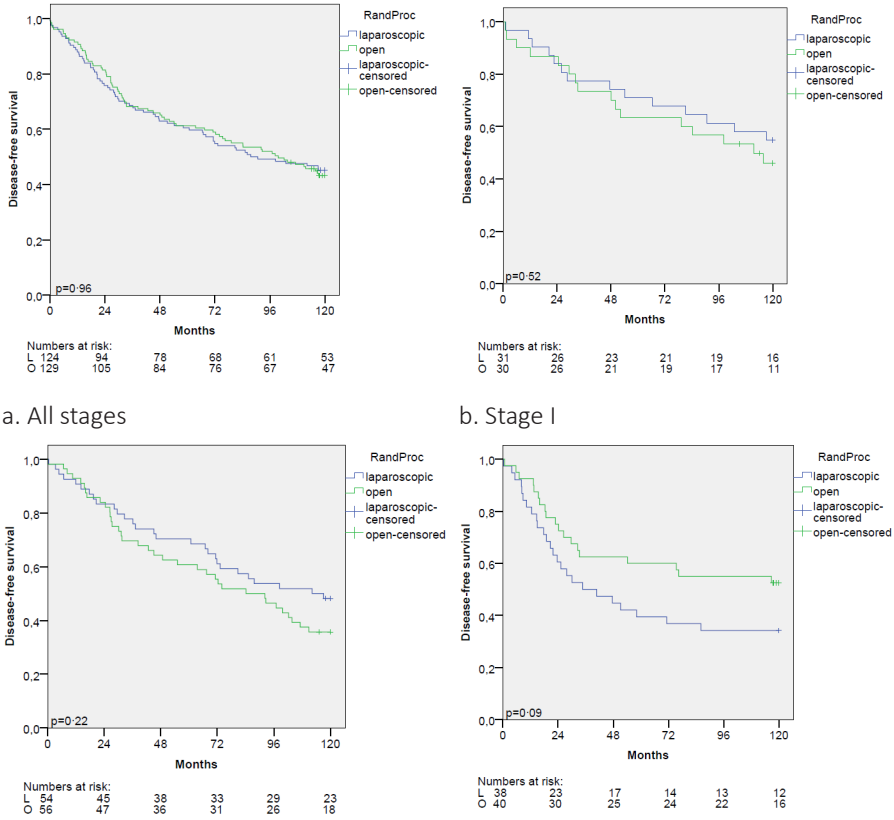


Table 1. Patient baseline characteristics

	Laparoscopic colectomy (n=131)	Open colectomy (n=140)	Total (n=271)
Age (years), median (range)	71 (54-84)	72 (54-84)	71 (54-84)
Gender, n (%)			
Male	63 (48.1)	76 (54.3)	139 (51.3)
Female	68 (51.9)	64 (45.7)	132 (48.7)
ASA group, n (%)			
I	44 (33.6)	49 (35.0)	93 (34.3)
II	62 (47.3)	73 (52.1)	135 (49.8)
III	20 (15.3)	18 (12.9)	38 (14.0)
Missing data	5 (3.8)	-	5 (1.8)
Body-mass index (kg/m²), median (range)	24.8 (20.2-29.6)	25.1 (20.2-30.7)	24.9 (20.2-29.9)

Range=10th to 90th percentile, ASA=American Society of Anesthesiologists classification

Figure 2. Disease-free survival



a. All stages

b. Stage I

c. Stage II

d. Stage III

Table 2. Operative and pathological data

	Laparoscopic colectomy (n=125)	Open colectomy (n=131)	Total (n=256)	p-value
Intervention, n (%)				0.527*
Right hemicolectomy	68 (54.4)	66 (50.4)	134 (52.3)	
Left hemicolectomy	10 (8.0)	10 (7.6)	20 (7.8)	
Sigmoidectomy	41 (32.8)	52 (39.7)	93 (36.3)	
Other	6 (4.8)	3 (2.3)	9 (3.5)	
Conversions				
Preoperative	6 (4.8)	-		
Intraoperative	34 (27.2)	-		
Duration of intervention (min), median (range)				
In theatre	180 (130-270)	135 (93.5-210)		<0.001∞
Skin to skin	140 (95-229.5)	95 (70-160.2)		<0.001∞
Blood loss (ml), median (range)	112.5 (13.5-559)	200 (50-825)		0.024∞
Size of tumour (cm), median (range)	4.0 (2.0-6.8)	4.0 (2.5-7.5)		0.168‡
Resection margins, n (%)				1.00*
Positive	1 (0.8)	2 (1.5)		
Negative	117 (99.2)	128 (98.5)		
Tumour stage, n (%)				0.974*
I	31 (25.0)	30 (23.4)	61 (24.2)	
II	54 (43.5)	57 (44.5)	111 (44.0)	
III	39 (31.5)	41 (32.0)	80 (31.7)	

Range=10th to 90th percentile, *=Fisher's exact test, ∞=Mann-Whitney U test, ‡=Students t test

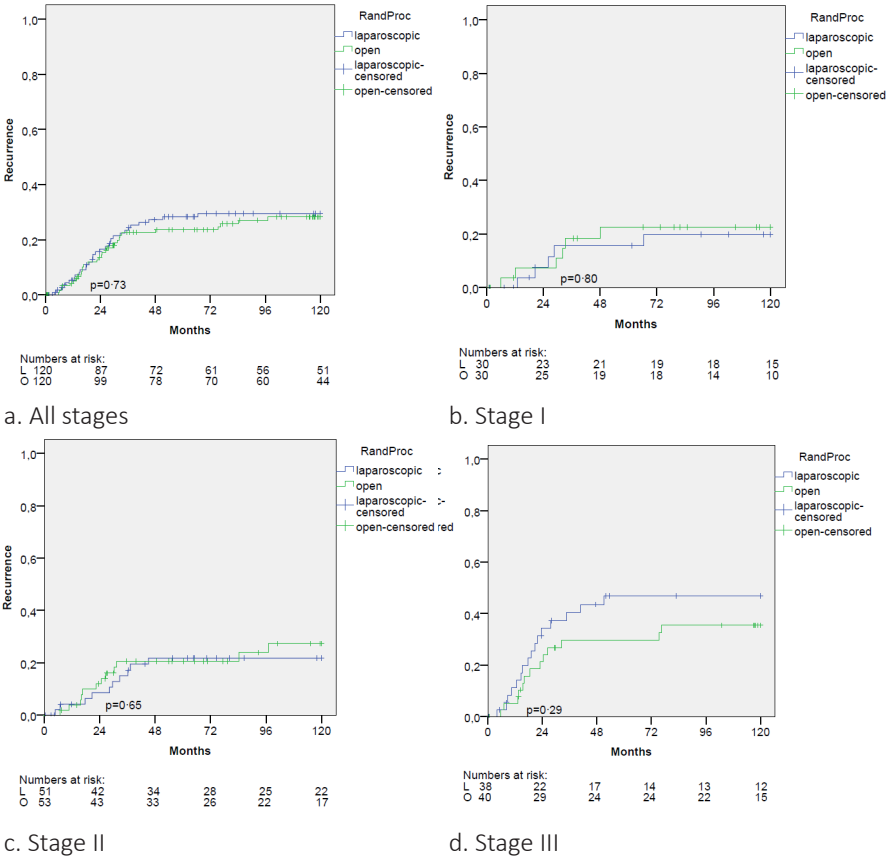
Overall survival

At 10-year follow-up 133 patients had died, 64 in the laparoscopic group and 69 in the open group. Fifty-three patients who died, had recurrent disease (27 patients in the laparoscopic group and 26 patients in the open group). The 10-year overall survival rate was 48.4% in the laparoscopic group and 46.7% in the open group (difference 1.7%; 95% CI, -10.6 to 14.0; p=0.83). In patients with stage I colon cancer, overall survival rates were 58.1% and 52.7% for the laparoscopic and open group respectively (difference 5.4%; 95% CI, -19.7 to 30.5; p=0.67). In patients with stage II disease these rates were 51.9% and 41.1% (difference 10.8%; 95% CI, -7.8 to 29.4; p=0.23) and in patients with stage III disease 36.8% in the laparoscopic group and 50.8% in the open group (difference -14.0%; 95% CI, -35.8 to 7.8; p=0.22) (Figure as supplementary material).

Recurrences

A total of 62 patients developed recurrent disease during the 10-year follow-up period, accounting for a recurrence rate of 29.4% in the laparoscopic group and 28.2% in the open group (difference 1.2%; 95% CI, -11.1 to 13.5; p=0.73). In patients with stage I colon cancer, recurrence rates were 19.8% and 22.5% for the laparoscopic and open group respectively (difference -2.7%; 95% CI, -25.2 to 19.8; p=0.80). In patients with stage II disease these rates were 21.8% and 27.3% (difference -5.5%; 95% CI, -23.7 to 12.7; p=0.65) and in patients with stage III disease 46.8% in the laparoscopic group and 35.4% in the open group (difference 11.4%; 95% CI, -11.6 to 34.4; p=0.29) (Figure 3).

Figure 3. Recurrence



a. All stages

b. Stage I

c. Stage II

d. Stage III

The site of recurrence did not significantly differ between the two groups. In total 43 patients suffered a locoregional recurrence, 23 patients in the laparoscopic group and 20 patients in the open group. Seven patients had a recurrence in the port- or wound-site, three patients in the laparoscopic and four patients in the open group. The time of occurrence of the port- and wound-site recurrences after surgery was in the laparoscopic group 8.1 months, 30.9 months, and 34.7 months and in the open group 16.0 months, 16.7 months, 27.5 and 31.2 months. In total 40 patients were diagnosed with a distant recurrence (19 in the laparoscopic and 21 in the open group), accounting for 69 distant recurrences (Table as supplementary material).

At 5 years follow-up, 154 patients were alive and free of disease. Between 5 and 10 years after surgery five of these 154 patients (3%) developed a first recurrence. Three other patients developed a recurrence between 5 and 10 years after surgery as well, however in these patients it was not the first recurrence.

Discussion

The survival and recurrence rates 10 years after either laparoscopic or open colectomy for cancer are similar. At 10 years after surgery for stage I, II and III colon cancer, disease-free survival rates were 45.2% and 43.2% in respectively the laparoscopic and open group. Overall survival rates were 48.4% and 46.7% for the laparoscopic and open group. Lacy et al. reported in 219 patients with colon cancer stage I-III at a median follow-up of 95 months similar cancer-free survival and overall survival rates between the laparoscopic and open groups as well.[4] Due to reduction of surgical trauma, minimally invasive surgery was expected to be associated with improved oncological outcomes.[14] However, this assumption has not been validated by current available evidence.

Only three percent of all patients that were free of disease and alive at 5 years developed a recurrence more than 5 years after index surgery. Merely two other studies on long-term survival after colon cancer surgery have been published. Similar patterns of recurrences were reported but exact numbers were not provided.[4,5] Hence, the current colon cancer guidelines recommendation to cease follow-up after 5 years after surgery, appears justified.

The intra-operative conversion rate of this substudy was 27%, which is higher than the 17% overall intra-operative conversion rate of the COLOR trial. Other large randomised trials reported conversion rates of 11%, 15%, 21% and 25%.[3,15-17] All these trials were conducted between 1993 and 2005. In those years, routine preoperative imaging of colonic cancer was limited in most patients to barium enema and ultrasonography of the liver.[2,14,15] In the COLOR trial imaging of the tumour was performed with computed tomography (CT) in 4% of the patients and with barium enema in 40% of the patients. In 81% of the patients a colonoscopy was done with tattooing of the tumour in 3%.[2] Nowadays, abdominal CT has become a standard component of the diagnostic workup in patients with colon cancer allowing preoperative identification of patients with large and invasive colonic carcinomas which are not amenable to laparoscopic surgery. In this study the reason for conversion was fixation of the tumour in one third of the patients and in one fourth the tumour could not be properly identified during the procedure, both as result of limitations in preoperative workup at the time this trial was conducted. The high rate of converted procedures may have been caused by limited technical skills among the surgeons, as well as deficiencies in the workup at that time, such as quality of the CT-scan and lack of inking of the tumour at endoscopy, which was not part of the standard preoperative procedure at that time.

Even though in this report all converted patients were analysed in the laparoscopic group according to the intention to treat principle, survival rates of the laparoscopic and open group did not differ. However, the impact of conversion on survival remains unclear. A recent report on 104 400 patients included in the American National Cancer Data Base concluded that conversion from laparoscopic to open surgery did not result in compromised oncologic outcomes.[18] On the contrary, the CLASICC trial showed worse overall survival in converted patients at a median follow-up of 63 months.[5]

Deposits of tumour cells at trocar sites (port-site metastases) were reported during the initial experience with laparoscopic colectomy for cancer.[19,20] These findings stalled implementation of laparoscopic surgery in the management of colon cancer for more than a decade. In this study, cancer recurrences in the abdominal wall were noted within 10 years after surgery in two percent of patients. All these recurrences occurred within 3 years after index surgery. In the CLASICC trial, 12 out of 641 (1.9%) analysed patients had one or more port- or wound-site recurrences, ten (2.3%) in the laparoscopic group and two (0.9%) in the open group, without a significant difference.[5] The COST trial reported among 863 analysed patients, surgical wound metastases as first site of recurrence in four patients (0.9%) in the laparoscopic group and two patients (0.5%) in the open group at 5 years.[21]

This report has several limitations. Firstly, follow-up until 10 years after index surgery was not part of the original protocol for the COLOR trial. This report only involves the Dutch patients of the COLOR trial representing one quarter of the entire study population. Although only a subgroup of patients was included, this study on long-term outcomes after colon cancer surgery involves one of the largest cohorts of patients reported to date. Furthermore, the primary outcome of the original study was disease-free survival at 3 years. This study was not powered for a 10-year follow-up period and the number of patients must have been larger according to an adequate power-analysis. Therefore, results as the high conversion rate of the Dutch population compared to the entire cohort should be interpreted with caution.

In conclusion, disease-free survival, overall survival, and recurrence rates at 10-year follow-up after laparoscopic and open resection of non-metastatic and non-invasive colon cancer were similar.

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Philippe Wittich, Eric Hazebroek, Mark Buunen, Ruben Veldkamp and Esther Kuhry coordinated the study and supervised the enrolment and follow-up of patients.

Disclosures

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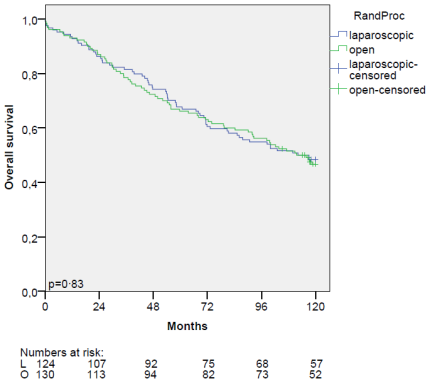
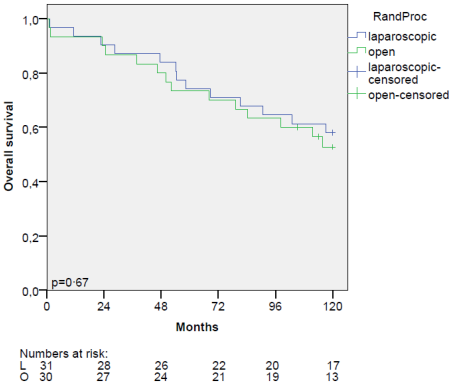
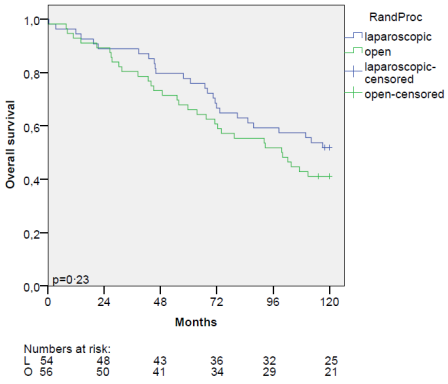
Supplementary figure. Overall survival



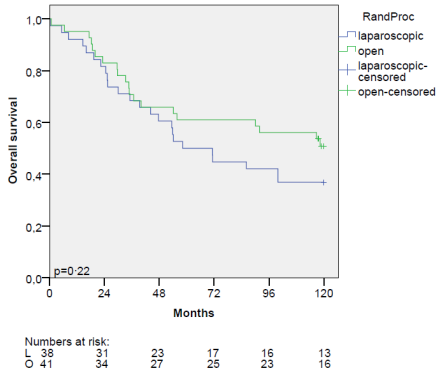
a. All stages



b. Stage I



c. Stage II



d. Stage III

Supplementary table. Pattern of recurrences in 62 patients

	Laparoscopic colectomy	Open colectomy	Overall
Number of total recurrences			
Locoregional	23	20	43
Peritoneum	3	2	5
Primary tumour site	17	14	31
Port- or wound-site	3	4	7
Liver	15	19	34
Lung	7	11	18
Adnex	2	2	4
Ossal	2	3	5
Brain	0	1	1
Spleen	1	1	2
Omentum	2	0	2
Lymph nodes	2	0	2
Pancreas	1	0	1
Total	**55**	**57**	**112**

CHAPTER 4

A randomized trial of laparoscopic versus open surgery for rectal cancer

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Abstract

Background Laparoscopic resection of colorectal cancer is widely used. However, robust evidence to conclude that laparoscopic surgery and open surgery have similar outcomes in rectal cancer is lacking. A trial was designed to compare 3-year rates of cancer recurrence in the pelvic or perineal area (locoregional recurrence) and survival after laparoscopic and open resection of rectal cancer.

Methods In this international trial conducted in 30 hospitals, we randomly assigned patients with a solitary adenocarcinoma of the rectum within 15 cm of the anal verge, not invading adjacent tissues, and without distant metastases to undergo either laparoscopic or open surgery in a 2:1 ratio. The primary end point was locoregional recurrence 3 years after the index surgery. Secondary end points included disease-free and overall survival.

Results A total of 1044 patients were included (699 in the laparoscopic-surgery group and 345 in the open-surgery group). At 3 years, the locoregional recurrence rate was 5.0% in the two groups (difference, 0 percentage points; 90% confidence interval [CI], -2.6 to 2.6). Disease-free survival rates were 74.8% in the laparoscopic-surgery group and 70.8% in the open-surgery group (difference, 4.0 percentage points; 95% CI, -1.9 to 9.9). Overall survival rates were 86.7% in the laparoscopic-surgery group and 83.6% in the open-surgery group (difference, 3.1 percentage points; 95% CI, -1.6 to 7.8).

Conclusions Laparoscopic surgery in patients with rectal cancer was associated with rates of locoregional recurrence and disease-free and overall survival similar to those for open surgery. (Funded by Ethicon Endo-Surgery Europe and others; COLOR II ClinicalTrials.gov number, NCT00297791.)

Colorectal cancer is the third most common cancer worldwide and accounts for nearly 1.4 million new cases and 694,000 deaths per year. Approximately one third of all colorectal cancers are localized in the rectum.[1-4] Less than a half century ago, rectal cancer had a poor prognosis, with cancer recurrence rates in the pelvic or perineal area (locoregional recurrence) of up to 40% and 5-year survival rates after surgical resection of less than 50%.[5,6] In the 1980s, Heald and Ryall[6] introduced a new surgical technique of complete removal of the fatty envelope surrounding the rectum (mesorectum), called total mesorectal excision. The adoption of total mesorectal excision combined with neoadjuvant chemoradiotherapy in selected patients has reduced locoregional recurrence rates to below 10% and improved cancer-free survival rates to more than 70%.[7-10]

Laparoscopic surgery has progressively replaced open colonic surgery in recent decades owing to favorable short-term outcomes, such as less pain, reduced blood loss, and improved recovery time.[11] Initially, there was concern regarding the safety of laparoscopic colectomy after reports of cancer recurrence in the abdominal wall.[12,13] In various trials in which patients with colon cancer were randomly assigned to undergo either open or laparoscopic surgery, evidence was obtained that laparoscopic surgery was associated with similar disease-free and overall survival rates as open surgery.[14,15] However, evidence is lacking from large, randomized clinical trials indicating that survival after laparoscopic resection of rectal cancer is not inferior to open surgery. We previously reported that laparoscopic surgery in patients with rectal cancer was associated with similar surgical safety and improved recovery time, as compared with open surgery.[16] In the Colorectal Cancer Laparoscopic or Open Resection (COLOR) II trial, we report the long-term rates of locoregional recurrence and survival in patients who were randomly assigned to undergo one of the two procedures.

Methods

Study design and oversight

The COLOR II trial was a noninferiority, open-label, multicenter trial conducted at 30 centers in 8 countries. The study was designed by members of the protocol committee. The local investigators and the trial manager gathered the data. The authors analyzed the data and vouch for the accuracy of the data and the analyses and the fidelity of the study to the protocol (available with the full text of this article at NEJM.org). The authors wrote the manuscript and made the decision to submit the manuscript for publication. The sponsor of the study, Ethicon Endo-Surgery Europe (a subsidiary of Johnson & Johnson), had no role in the study design, data gathering, analyses and interpretation, or writing of the manuscript.

Patients

Patients with a solitary adenocarcinoma of the rectum within 15 cm from the anal verge without distant metastases who were candidates for elective surgery were eligible for inclusion. The localization of the tumor was categorized as the upper rectum (distal border of tumor, 10 to 15 cm from the anal verge), middle rectum (5 to 10 cm from the anal verge), or lower rectum (<5 cm from the anal verge). Patients with T4 tumors or T3 tumors within 2 mm of the endopelvic fascia, as determined on computed tomography (CT) or magnetic resonance imaging (MRI), were excluded. Other exclusion criteria have been reported previously.[16] The study was approved by the institutional review board at each participating center. All patients provided written informed consent.

Randomization

Randomization was performed at the patient level. Laparoscopic and open surgery were performed at all participating centers. Eligible patients were randomly assigned in a 2:1 ratio to undergo either laparoscopy or open surgery according to a list of randomization numbers with treatment assignments. This list was computer-generated, with stratification according to hospital, tumor location, and the presence or absence of preoperative radiotherapy. An Internet application allowed central randomization.

Procedures and quality control

The use of neoadjuvant therapy was determined by multidisciplinary cancer boards at each participating hospital, according to local standards, without differences between the laparoscopic-surgery group and the open-surgery group. All procedures were required to comply with the principles of total mesorectal excision or partial mesorectal excision if the cancer was

located in the upper part of the rectum.[6]

The selection of centers for participation in the trial was based on stringent quality assessment by the study management committee to confirm the use of proper surgical technique. Unedited recordings of five consecutive laparoscopic total mesorectal excisions were evaluated. The respective pathology reports of these five consecutive cases were reviewed to confirm completeness of the specimens. Pathologists adhered to standardized processing and assessment of specimens, as described in detail in the trial protocol, to ensure accurate reporting by all participating centers.[16] The circumferential resection margin was defined as "involved" when tumor cells were present within 2 mm from the lateral surface of the mesorectum.

End points

The primary end point was locoregional recurrence 3 years after the index surgery. Secondary end points included disease-free and overall survival.

Follow-up

Minimal required follow-up included annual clinical examinations for 5 years after surgery. Three years after the index surgery, CT or MRI of the pelvis combined with imaging of the liver and the chest were performed. Recurrent disease was defined as the presence of locoregional recurrence, the presence of distant metastases, or death from rectal cancer.

Statistical analysis

We used the Kaplan-Meier method to estimate the difference in recurrence rates between the two study groups at 3 years postoperatively. Laparoscopic surgery was considered to be noninferior to open surgery if the one-sided 95% confidence interval for the difference in locoregional recurrence rates excluded an absolute difference of 5 percentage points or more. With 1000 patients who could be evaluated at a ratio of 2:1, the power of the noninferiority test was 80% at a locoregional recurrence rate of 10% in the open-surgery group.

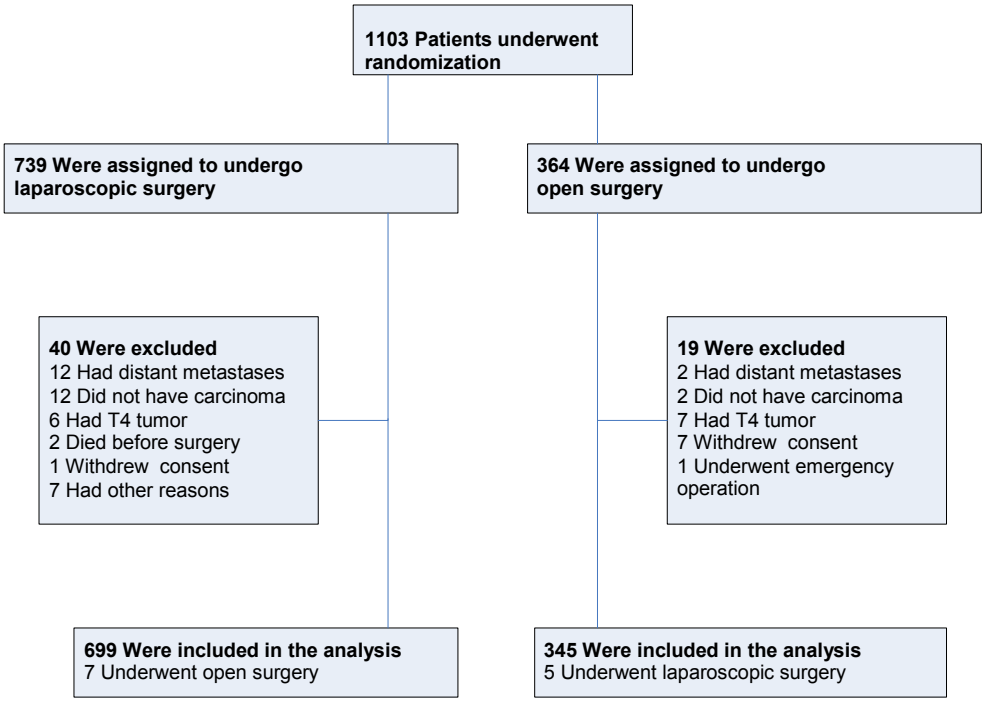
All analyses were performed on an intention-to-treat basis. We used the Kaplan-Meier method to compare rates of recurrence, disease-free survival, and overall survival at 3 years. The one-sided 95% confidence interval for the between group difference in locoregional recurrence corresponds to the upper limit of the two-sided 90% confidence interval for this difference. For survival rates, two-sided 95% confidence intervals were calculated. In addition, we performed as-treated analyses for locoregional recurrence, disease-free survival, and overall survival.

Results

Patients

From January 2004 through May 2010, a total of 1103 patients with rectal cancer underwent randomization. Of these patients, 739 were assigned to undergo laparoscopic surgery and 364 to undergo open surgery. After the exclusion of 59 patients following randomization, 1044 patients (699 in the laparoscopic-surgery group and 345 patients in the open-surgery group) were included in the analysis (Fig. 1). In total, 1036 patients were included in the long-term analyses.

Figure 1. Flowchart



At the 3-year follow-up, data were available for 771 patients (74%) regarding locoregional recurrence, 923 (89%) regarding disease-free survival, and 903 (87%) regarding overall survival. The clinical characteristics of the patients were similar in the two groups, as were the proportions of patients who received neoadjuvant chemoradiotherapy (Table 1).

Table 1. Baseline clinical characteristics and pathology

	Laparoscopic surgery (n=699)	Open surgery (n=345)
Sex		
Male	448/699 (64%)	211/345 (61%)
Female	251/699 (36%)	134/345 (39%)
Age - years (SD)	66.8 (10.5)	65.8 (10.9)
American Society of Anesthesiologists classification		
I	156/678 (23%)	65/338 (19%)
II	386/678 (57%)	211/338 (62%)
III	131/678 (19%)	61/338 (18%)
IV	5/678 (<1%)	1/338 (<1%)
Missing data	21/699 (3%)	7/345 (2%)
Body-mass index - kg/m^2 (SD)	26.1 (4.5)	26.5 (4.7)
Location of tumor (distance from anal verge)		
Upper rectum (10-15 cm)	223/699 (32%)	116/345 (34%)
Middle rectum (5-10 cm)	273/699 (39%)	136/345 (39%)
Lower rectum (<5 cm)	203/699 (29%)	93/345 (27%)
Clinical stage		
I	201/667 (30%)	96/329 (29%)
II	209/667 (31%)	107/329 (33%)
III	257/667 (38%)	126/329 (38%)
Missing data	32/699 (5%)	16/345 (5%)
Preoperative radiotherapy	412/699 (59%)	199/345 (58%)
Preoperative chemotherapy	196/609 (32%)	99/295 (34%)
Missing data	90/699 (13%)	50/345 (14%)
No residual tumor‡	33/412 (8%)	19/199 (10%)
Missing data	18/699 (3%)	3/345 (<1%)
Pathology stage§		
I	231/681 (34%)	107/342 (31%)
II	180/681 (26%)	91/342 (27%)
III	233/681 (34%)	125/342 (37%)
IV	4/681 (<1%)	0
Missing data	18/699 (3%)	3/345 (<1%)
Macroscopic completeness of resection		
Complete	589/666 (88%)	303/331 (92%)
Partially complete	58/666 (9%)	19/331 (6%)

Table 1. Continued.

	Laparoscopic surgery (n=699)	Open surgery (n=345)
Incomplete	19/666 (3%)	9/331 (3%)
Missing data	33/699 (5%)	14/345 (4%)
Lymph nodes harvested	13 (10-18)	14 (10-19)
Missing data	16/699 (2%)	4/345 (1%)

Data are n/N (%), median (IQR) or mean (SD).
‡ The denominator is the number of patients who received preoperative radiotherapy.
§ The patients with no residual tumor were not included in the analysis of pathological stage.

Short-term outcomes

Five patients who were randomly assigned to the open-surgery group underwent laparoscopic surgery. Of these patients, three requested laparoscopic surgery after randomization, and the reason for crossover was unknown for the other two patients. In addition, seven patients in the laparoscopic- surgery group underwent open surgery: one owing to poor pulmonary condition, five because no laparoscopic surgeon was available, and one for an unknown reason. A total of 86% of laparoscopic and open procedures were performed by surgeons who had performed both laparoscopic and open surgeries for rectal cancer. The conversion rate from laparoscopic surgery to open surgery was 16%. In the laparoscopic-surgery group, the operating time was 52 minutes longer, bowel function returned 1 day earlier, and the hospital stay was 1 day shorter than in the open-surgery group. There were no significant differences in the rates of anastomotic leaking, complication, or death.[16]

Pathological analyses

There were no significant between-group differences for all lesions with respect to macroscopic completeness of the mesorectum, involved circumferential resection margins (Tables 1 and 2), or distal resection margins (median, 3.0 cm in the two groups).

Locoregional recurrence

At 3 years, the rate of locoregional recurrence was 5.0% in each of the study groups (31 patients in the laparoscopic-surgery group and 15 in the open-surgery group) (Table 2). The upper limit of the 90% confidence interval for the absolute between-group difference in the rate of locoregional recurrence (2.6 percentage points) was below the noninferiority margin of 5 percentage points. In the intention-to-treat analysis, rates of locoregional recurrence of upper rectal cancers were 3.5% in the laparoscopic-surgery group and 2.9% in the open-surgery group (difference, 0.6 percentage points; 90% CI, -2.9 to 4.1). In patients with middle

Table 2. Involved circumferential resection margin and locoregional recurrence

		Involved CRM*	Difference of involved CRM (95% CI)	Locoregional recurrence as randomized	Difference of locoregional recurrence as randomized (90% CI)	Locoregional recurrence as treated	Difference of locoregional recurrence as treated (90% CI)
Total group	laparoscopic surgery	56/588 (10%)	-0.5% (-4.9% to 3.5%)	5.0%	0% (-2.6% to 2.6%)	4.3%	-2.0% (-4.7% to 0.7%)
	open surgery	30/300 (10%)		5.0%		6.3%	
Upper rectum	laparoscopic surgery	18/196 (9%)	-0.1% (-8.2% to 6.4%)	3.5%	0.6% (-2.9% to 4.1%)	3.0%	-0.9% (-4.6% to 2.8%)
	open surgery	9/97 (9%)		2.9%		3.9%	
Middle rectum	laparoscopic surgery	22/228 (10%)	6.2% (0.1% to 11.2%)	6.5%	4.1% (0.7% to 7.5%)	5.7%	1.6% (-2.3% to 5.5%)
	open surgery	4/115 (3%)		2.4%		4.1%	
Lower rectum	laparoscopic surgery	15/164 (9%)	-12.4% (-23.2% to -3.0%)	4.4%	-7.3% (-13.9% to -0.7%)	3.8%	-8.9% (-15.6% to -2.2%)
	open surgery	17/79 (22%)		11.7%		12.7%	

*Data are n/N (%). CRM=circumferential resection margin.
*Denominator was the number of patients without complete remission.
CI=confidence interval.

rectal cancers, locoregional recurrence rates were 6.5% and 2.4%, respectively (difference, 4.1 percentage points; 90% CI, 0.7 to 7.5); in patients with lower rectal cancers, the rates were 4.4% and 11.7%, respectively (difference,-7.3 percentage points; 90% CI,-13.9 to -0.7).

In the as-treated analysis, the locoregional recurrence rates in patients with upper rectal cancers were 3.0% in the laparoscopic-surgery group and 3.9% in the open-surgery group (difference, -0.9 percentage points; 90% CI, -4.6 to 2.8). In patients with middle rectal cancers, locoregional recurrence rates were 5.7% and 4.1%, respectively (difference, 1.6 percentage points; 90% CI,-2.3 to 5.5); in patients with lower rectal cancers, the rates were 3.8% and 12.7%, respectively (difference,-8.9 percentage points; 90% CI,-15.6 to -2.2). Among 46 patients with locoregional recurrence at 3 years, 27 patients had distant metastases as well.

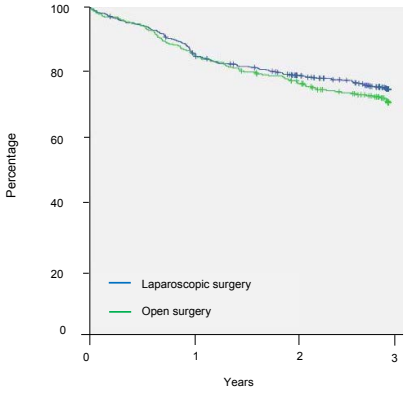
Disease-free and overall survival

At 3 years, the rate of disease-free survival was 74.8% in the laparoscopic-surgery group and 70.8% in the open-surgery group (difference, 4.0 percentage points; 95% CI,-1.9 to 9.9) (Fig. 2). In patients with stage I or II rectal cancer, rates of disease-free survival were similar in the two groups, whereas in patients with stage III disease, the rate of disease-free survival was 64.9% in the laparoscopic-surgery group and 52.0% in the open-surgery group (difference, 12.9 percentage points; 95% CI, 2.2 to 23.6).

At 3 years after surgery, 145 patients had died, accounting for an overall survival rate of 86.7% in the laparoscopic-surgery group and 83.6% in the open-surgery group (difference, 3.1 percentage points; 95% CI,-1.6 to 7.8) (Fig. 3). Overall survival rates according to disease stage were also similar in the two groups.

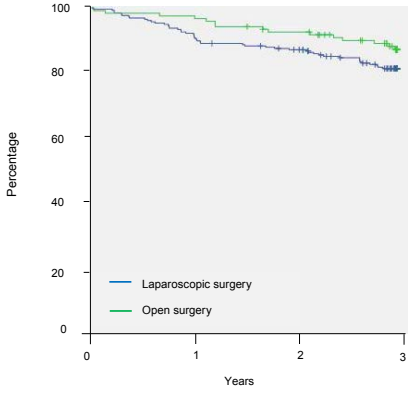
Distant metastases at 3 years after surgery were reported in 19.1% of the patients in the laparoscopic-surgery group and 22.1% of those in the open-surgery group, including one port-site metastasis in the laparoscopic-surgery group and one tumor recurrence in the laparotomy wound in the open-surgery group.

Figure 2. Disease-free survival



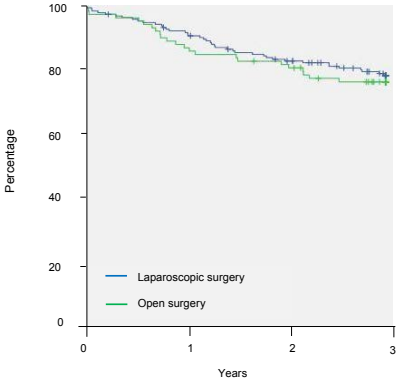
Number at risk				
Laparoscopic surgery	692	604	536	441
Open surgery	344	297	264	211

a. All stages



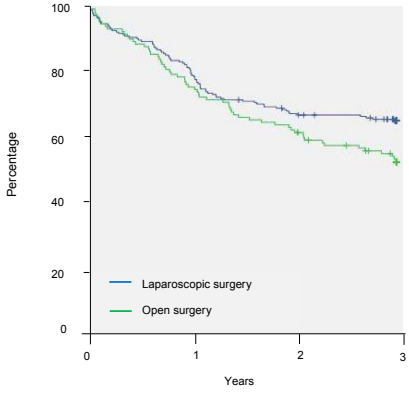
Number at risk				
Laparoscopic surgery	247	227	210	169
Open surgery	117	114	106	85

b. Stage I



Number at risk				
Laparoscopic surgery	187	170	150	126
Open surgery	92	80	74	61

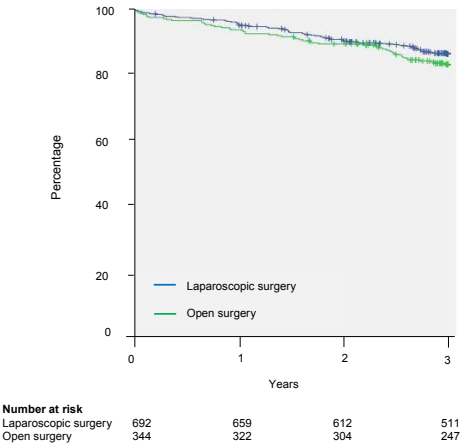
c. Stage II



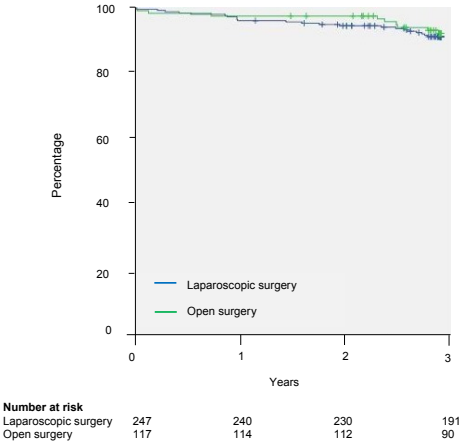
Number at risk				
Laparoscopic surgery	230	181	151	129
Open surgery	124	93	75	57

d. Stage III

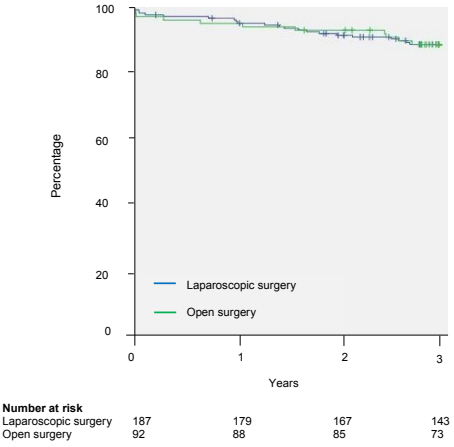
Figure 3. Overall survival



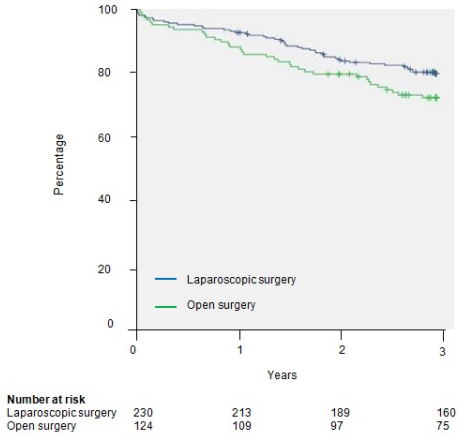
a. All stages



b. Stage I



c. Stage II



d. Stage III

Discussion

In this trial, we compared the rates of locoregional recurrence of rectal cancer after laparoscopic or open resection. Locoregional recurrences were recorded in 5.0% of the patients in each of the two groups. In the Dutch trial of total mesorectal excision by Kapiteijn et al.,[8] among 1805 patients with rectal cancer who underwent open resection, the locoregional recurrence rate at 2 years was 5.3%, a rate similar to that in our study.

In the Conventional versus Laparoscopic Assisted Surgery in Colorectal Cancer (CLASICC) trial, the first multicenter, randomized study to determine the effect of laparoscopic surgery on rectal-cancer outcomes involving 381 patients, the locoregional recurrence rate at 3 years was 9.7% after laparoscopic surgery and 10.1% after open surgery.[17] The presence of involved circumferential resection margins, which predispose patients to locoregional recurrence, were observed in 16% of the patients after laparoscopic surgery in the CLASICC trial, as compared with 10% of those in the laparoscopic surgery group in our study.[18,19] Recently, in the Comparison of Open versus Laparoscopic Surgery for Mid or Low Rectal Cancer after Neoadjuvant Chemoradiotherapy (COREAN) study[10] involving 340 patients with cancer of the middle or lower rectum who had received preoperative chemoradiotherapy, rates of locoregional recurrence were 2.6% after laparoscopic surgery and 4.9% after open surgery. The presence of involved circumferential resection margins in the COREAN trial (2.9% after laparoscopic surgery and 4.1% after open surgery) were lower than those in our study.[20] However, we considered circumferential resection margins as being involved when tumor cells were present within 2 mm from the lateral surface of the mesorectum, whereas the COREAN study group used a 1-mm margin. The use of a 2-mm margin yields a higher rate of involved circumferential resection margins.[16]

In our study, laparoscopic surgery in patients with cancer in the lower third of the rectum was associated with a lower rate of involved circumferential resection margin and a lower locoregional recurrence rate than was open surgery. During laparoscopic surgery, narrow spaces such open surgery owing to the use of a laparoscope, which projects a magnified and well-illuminated image of the operative field on the monitors. A clear view is of paramount importance to accomplish a resection of the cancer with sufficient margins. As a result of tapering of the mesorectum at the level of the pelvic floor, tissue margins around low rectal cancers are smaller than those around tumors located in the middle or upper rectum, which predisposes such tumors to incomplete radical resection.[21] Therefore, a procedure called extralevatory abdominoperineal rectum extirpation (ELAPE), in which a part of the pelvic

floor musculature is resected through a perineal approach, has been introduced. During the past decade, the ELAPE principle was introduced but was not included in the COLOR II study protocol.[22] However, the debate on the value of this technique continues.

The disease-free survival rates at 3 years in our study were 74.8% after laparoscopic surgery and 70.8% after open surgery, as compared with rates of 79.2% and 72.5%, respectively, during the same follow-up period in the COREAN study.[10] In our study, among patients with stage III disease, disease-free survival rates were 64.9% after laparoscopic surgery and 52.0% after open surgery. A similar finding was reported by Lacy and colleagues[15] among patients who underwent laparoscopic resection of lymph-node-positive colon cancers. These observations may confirm the experimental findings that less surgical trauma associated with the use of laparoscopic techniques reduces tumor recurrence.[23] In a study involving patients undergoing laparoscopic and open colonic resection, laparoscopic surgery was followed by attenuated stress responses and improved preservation of immune function.[24] Further studies are necessary to determine whether laparoscopic surgery for cancer is associated with improved survival.

The size of the cohort in our study allowed for the use of a noninferiority margin of 5 percentage points, whereas in the smaller COREAN trial, the noninferiority margin was 15 percentage points.[20] Since centers in eight countries in Europe, North America, and Asia participated in our study, the outcomes appear to be applicable to surgical practice in general.

Rectal-cancer surgery, regardless of which technique is used, is technically demanding and requires sufficient training to be performed safely. We verified the surgical quality of laparoscopic total mesorectal excision by reviewing unedited recordings of five consecutive laparoscopic procedures for each center. Laparoscopic surgical expertise is difficult to measure objectively but is reflected to a certain extent by operative time and conversion rate.[25] The median operating times for laparoscopic procedures were 240 minutes in our study and 245 minutes in the COREAN trial; the latter obviously was recorded by highly skilled surgeons, given the low conversion rate of only 1% in that study.[20] The conversion rate in our study remained 16% throughout the study period, whereas a decline in the conversion rate from 38% in the first year to 16% in the last year of the trial was reported by the CLASICC group.[19]

In our study, patients with T4 and T3 lesions within 2 mm of the endopelvic fascia were excluded because laparoscopic resection of these large tumors is very difficult and could result in less-than-complete resection with subsequent higher rates of locoregional recurrence.

Therefore, we do not recommend laparoscopic surgery in patients with T4 or T3 rectal cancers with threatened circumferential margins.

A limitation of our study is the absence of centralized macroscopic and microscopic evaluation of the resected specimens. However, all pathologists adhered to a detailed standardized protocol. Another limitation is the use of different imaging methods to determine the location of the tumor. It would have been preferable to standardize the imaging technique of the pelvis and calibrate the measurements centrally by independent professionals.

Some surgeons insert one of their hands through a gastight port in the abdomen during laparoscopic colorectal surgery to allow for manual retraction of tissues and tactile feedback, a procedure called hand-assisted laparoscopic surgery.[26] The group who designed the study thought that a hand would obstruct the laparoscopic view of the narrow pelvis, so this technique was not part of the current protocol.

In conclusion, long-term outcomes of the COLOR II trial indicate that laparoscopic surgery is as safe and effective as open surgery in patients with rectal cancers without invasion of adjacent tissues.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Appendix

Reply to: 'Comment on: "A Randomized Trial of Laparoscopic versus Open Surgery for Rectal Cancer"'

Bonjer HJ, Deijen CL, Haglind E; COLOR II Study Group.

N Engl J Med. 2015 Jul 9;373(2):194.

We agree with Kearney and Coffey that adjuvant chemotherapy could affect the rates of locoregional recurrence of rectal cancer. In our study, preoperative and postoperative protocols were administered equally in the laparoscopic-surgery group and the open-surgery group. [1] Adjuvant chemotherapy was administered in 32.4% of patients in the laparoscopic-surgery group and in 33.6% of patients in the open-surgery group. Since the rates of adjuvant chemotherapy were similar in the two study groups, between-group differences in outcome cannot be attributed to adjuvant chemotherapy.

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CHAPTER 5

Long-term outcomes of a randomized trial of laparoscopic versus open surgery for rectal cancer

COLOR II Study Group.

In preparation for publication (content under embargo).

Abstract

Background The debate on the role of laparoscopic surgery for rectal cancer continues. In most reports from randomized rectal cancer trials follow-up is limited to 3 years after surgery. However, development of recurrences is not limited to this period. The aim of this study was to provide data at 5 years after either laparoscopic or open surgery in patients with rectal cancer.

Methods In this noninferiority, multicenter trial patients with stage I-III rectal cancer within 15 cm from the anal verge and no distant metastases were randomized to either laparoscopic or open resection. Recurrence rates, disease-free survival and overall survival and follow-up rates were assessed using Kaplan-Meier estimates and their standard errors at 5 years after index-surgery.

Results A total of 1044 patients were included, 699 in the laparoscopic-surgery group and 345 in the open-surgery group. At 5 years, the locoregional recurrence rate was 6.4% in the laparoscopic-surgery group and 6.9% in the open-surgery group (difference, -0.5 percentage points; 90% confidence interval [CI], -4.0 to 3.0). Disease-free survival rates were 68.8% in the laparoscopic-surgery group and 65.1% in the open-surgery group (difference, 3.7 percentage points; 95% CI, -2.5 to 9.9). Overall survival rates were 78.5% in the laparoscopic-surgery group and 74.0% in the open-surgery group (difference, 4.5 percentage points; 95% CI, -1.2 to 10.2).

Conclusions Laparoscopic and open surgery in patients with noninvasive and nonmetastatic rectal cancer result in similar survival and recurrence rates at 5 years postoperatively. (Funded by Ethicon Endo-Surgery Europe and others; COLOR II ClinicalTrials.gov number, NCT00297791.)

Survival is one of the most important outcomes in the treatment of patients with rectal cancer. However, the debate on the role of laparoscopic surgery continues. Few large randomized trials have reported similar survival outcomes after laparoscopic resection of rectal cancer compared to conventional open resection.[1,2] Previously, we reported similar rates of 5% cancer recurrence in the pelvic or perineal area (locoregional recurrence) 3 years after either laparoscopic or open surgery. No differences in overall survival between the two treatment groups were reported as well. In patients with lymph-node-positive rectal cancer improved disease-free survival was observed after laparoscopic surgery compared to open surgery.[3] Therefore, noninferiority of laparoscopic surgery for rectal cancer was firmly confirmed.

However, development of recurrences is not limited to 3 years postoperatively.[2,4] Unfortunately, reports from randomized rectal cancer trials after 3 years follow-up are scarce. Only four of the published randomized trials comparing laparoscopic and open surgery in patients with rectal cancer (including a total of 684 laparoscopically operated patients) report results at 5 years follow-up or more.[4-9]

Furthermore, recently two other large randomized trials could not establish noninferiority of laparoscopic surgery for rectal cancer. Both trials questioned the safety of laparoscopic surgery in terms of adequate surgical resection stressing the need for long-term follow-up results.[10,11]

To provide long-term data and support our previously published conclusions, here we report outcomes of the Colorectal Cancer Laparoscopic or Open Resection (COLOR) II trial at 5 years after either laparoscopic or open surgery in patients with rectal cancer.

Methods

Study design and oversight

The COLOR II trial is a noninferiority, open-label, multicenter trial randomizing patients with stage I-III rectal cancer to either laparoscopic or open resection. The primary endpoint, locoregional recurrence at 3 years after the index surgery, has been reported previously.[3] The study was designed by members of the protocol committee. The local investigators and the trial manager gathered the data. The data were analyzed by the authors, including a statistician. All authors vouch for the accuracy of the data and analyses as well as the fidelity of the conduct of the study to the protocol. The authors wrote the paper and decided to publish. The sponsor of the study, Ethicon Endo-Surgery Europe (a subsidiary of Johnson & Johnson), had no role in study design, data gathering, analyses and interpretation or writing of the report.

Patients

The COLOR II trial was conducted in 30 hospitals in eight different countries. Main inclusion criterion was solitary adenocarcinoma of the rectum within 15 cm from the anal verge and no evidence of distant metastases. Tumor location was defined as upper (distal border of tumor 10-15 cm from the anal verge), middle (5-10 cm) or lower rectum (<5 cm). Main exclusion criteria were T4 tumors or T3 tumors within 2 mm of the endopelvic fascia, determined by CT or MRI. Other inclusion and exclusion criteria have been reported earlier.[12] The institutional review board of each participating center approved the study protocol, including 5-year follow-up. Written informed consent was obtained from all patients.

Randomization

Randomization was performed in a 2:1 ratio to laparoscopic or open surgery and carried out at the patient level. Laparoscopic and open surgery were both available in all participating hospitals. Randomization was performed centrally through an internet application according to a list of randomization numbers with treatment allocation. This list was computer-generated and stratified for participating center, gender, tumor location and neoadjuvant radiotherapy.

Procedures and quality control

Neoadjuvant therapy was applied according to local standards and determined by multidisciplinary cancer boards at all participating centers. Distribution was equal between the laparoscopic and open surgery groups. All procedures had to adhere to the principles of total mesorectal excision or partial mesorectal excision in the case of tumors located in the upper part of the rectum.[13]

The stringent quality assessment has been described in detail earlier.[12] In brief, unedited recordings of 5 consecutive laparoscopic total mesorectal excisions were evaluated by the study management committee as well as the respective pathology reports.

Endpoints

The primary endpoint was locoregional recurrence at 3 years postoperatively. Secondary outcomes were morbidity, mortality, disease-free and overall survival and recurrence at 5 years after index surgery.

Follow-up

Follow-up included at least clinical examinations every year during the first 5 years postoperatively. CT or MRI of the pelvis combined with imaging of liver and chest were mandatory at 3 years after index surgery. The definition of recurrent disease was evidence of locoregional recurrence or distant metastases, or death caused by rectal cancer.

Statistical analysis

Laparoscopic surgery was considered to be noninferior to open surgery if the one-sided 95% confidence interval for the difference in locoregional recurrence rates excluded a difference of 5 percentage points or more in favor of the control group. With a total of 1000 evaluable patients after 3 years follow-up, randomized at a ratio of 2 (laparoscopic) : 1 (open), the power of the noninferiority test was 80% at a locoregional recurrence rate of 10% in the open-surgery group. For 5 year outcomes, recurrence rates, disease-free survival and overall survival and follow-up rates were assessed using Kaplan-Meier estimates and their standard errors at 5 years after index-surgery. Because of the noninferiority design of the trial, the one sided 95% confidence interval for the between-group difference in locoregional recurrence corresponds to the upper limit of the two-sided 90% confidence interval for this difference. Two-sided 95% confidence intervals were calculated for the differences in survival rates between the two groups at 5 years after index-surgery. All analyses were performed according to the intention-to-treat principle. Furthermore, as-treated analyses were performed for locoregional recurrence, disease-free survival, and overall survival.

Results

Between January 2004 and May 2010, 1103 patients with rectal cancer were randomized. After excluding 59 patients, 1044 patients were included in the trial (699 in the laparoscopic-surgery group and 345 in the open-surgery group) (Figure 1). At 5-year follow-up, numbers at risk plus number of patients with an event were 642 for locoregional recurrence (61%), 865 for disease-free survival (83%) and 841 for overall survival (81%). In Table 1 the baseline characteristics of the patients and pathology results are given.

Table 1. Baseline characteristics and pathology

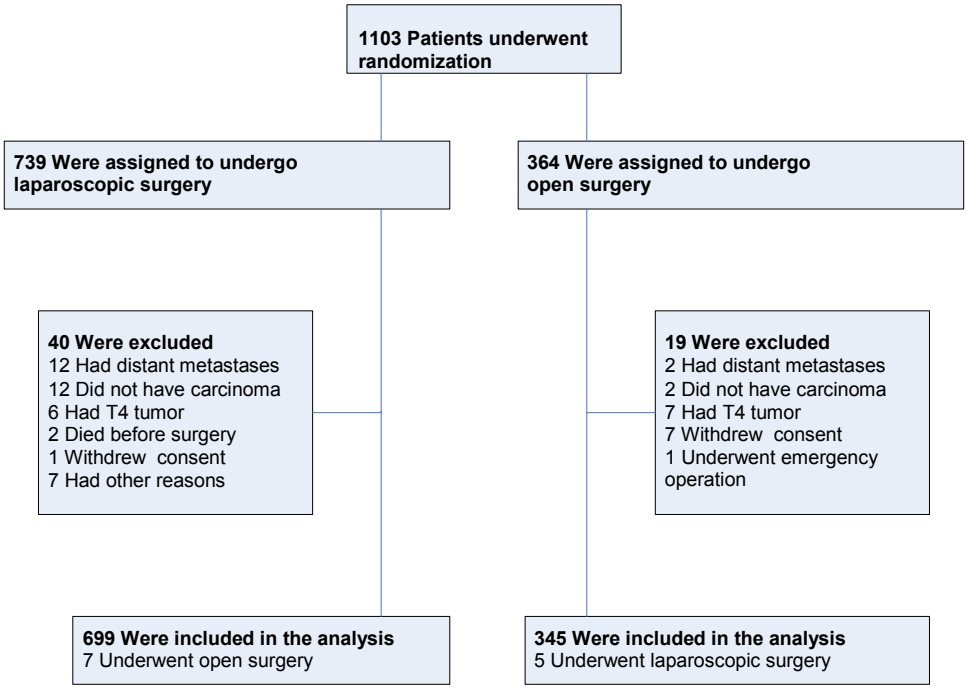
	Laparoscopic surgery (n=699)	Open surgery (n=345)
Sex		
Male	448/699 (64%)	211/345 (61%)
Female	251/699 (36%)	134/345 (39%)
Age - years (SD)	66.8 (10.5)	65.8 (10.9)
American Society of Anesthesiologists classification		
I	156/678 (23%)	65/338 (19%)
II	386/678 (57%)	211/338 (62%)
III	131/678 (19%)	61/338 (18%)
IV	5/678 (<1%)	1/338 (<1%)
Missing data	21/699 (3%)	7/345 (2%)
Body-mass index - kg/m^2 (SD)	26.1 (4.5)	26.5 (4.7)
Location of tumor (distance from anal verge)		
Upper rectum (10-15 cm)	223/699 (32%)	116/345 (34%)
Middle rectum (5-10 cm)	273/699 (39%)	136/345 (39%)
Lower rectum (<5 cm)	203/699 (29%)	93/345 (27%)
Clinical stage		
I	201/667 (30%)	96/329 (29%)
II	209/667 (31%)	107/329 (33%)
III	257/667 (38%)	126/329 (38%)
Missing data	32/699 (5%)	16/345 (5%)
Preoperative radiotherapy	412/699 (59%)	199/345 (58%)
Preoperative chemotherapy	196/609 (32%)	99/295 (34%)
Missing data	90/699 (13%)	50/345 (14%)
No residual tumor‡	33/412 (8%)	19/199 (10%)
Missing data	18/699 (3%)	3/345 (<1%)

Table 1. Continued

	Laparoscopic surgery (n=699)	Open surgery (n=345)
Pathology stage§		
I	231/681 (34%)	107/342 (31%)
II	180/681 (26%)	91/342 (27%)
III	233/681 (34%)	125/342 (37%)
IV	4/681 (<1%)	0
Missing data	18/699 (3%)	3/345 (<1%)
Macroscopic completeness of resection		
Complete	589/666 (88%)	303/331 (92%)
Partially complete	58/666 (9%)	19/331 (6%)
Incomplete	19/666 (3%)	9/331 (3%)
Missing data	33/699 (5%)	14/345 (4%)
Lymph nodes harvested	13 (10-18)	14 (10-19)
Missing data	16/699 (2%)	4/345 (1%)

Data are n/N (%), median (IQR) or mean (SD).
‡ The denominator is the number of patients who received preoperative radiotherapy.
§ The patients with no residual tumor were not included in the analysis of pathological stage.

Figure 1. Flowchart



Locoregional recurrence

At 5 years after surgery, in total 59 patients had developed a local recurrence, accounting for an overall locoregional recurrence rate of 6.5% (Table 2). There was no significant difference between the laparoscopic-surgery group (n=39, 6.4%) and open-surgery group (n=20, 6.9%) (difference,-0.5 percentage points; 90% CI,-4.0 to 3.0). In patients with upper rectal cancer the locoregional recurrence rate was 4.0% in both treatment groups (difference, 0 percentage points; 90% CI, -4.8 to 4.8). In patients with middle rectal tumors, the rates were 7.7% in the laparoscopic-surgery group and 4.6% in the open-surgery group (difference, 3.1 percentage points; 90% CI,-2.2 to 8.4). In patients with cancer of the lower one third of the rectum, locoregional recurrence rates were 7.0% and 14.1%, respectively (difference, -7.1 percentage points; 90% CI,-15.9 to 1.7).

In as-treated analysis, in patients with upper rectal cancer rates of locoregional recurrence were 3.5% and 5.0% for the laparoscopic-surgery and open-surgery group (difference,-1.5 percentage points; 90% CI,-6.5 to 3.5); in patients with middle rectal tumors the rates were 6.9% and 6.3%, respectively (difference, 0.6 percentage points; 90% CI,-5.1 to 6.3) and in patients with lower rectal cancer locoregional recurrence rates were 6.5% and 15.1% for the laparoscopic-surgery group and open-surgery group (difference, -8.6 percentage points; 90% CI,-17.3 to 0.1).

Disease-free survival

At 5 years after surgery, the disease-free survival rate was 68.8% in the laparoscopic-surgery group and 65.1% in the open-surgery group (difference, 3.7 percentage points; 95% CI,-2.5 to 9.9). In patients with stage I or II rectal cancer disease-free survival rates in the laparoscopic-surgery group and open-surgery group were similar; in patients with stage III disease, the rates were 58.4% and 46.8%, respectively (difference, 11.6 percentage points; 95% CI, 0.7 to 22.5) (Figure 2).

In as-treated analysis, the rates of disease-free survival were similar between the two treatment groups regarding all stages as well as in patients with stage I or stage II rectal cancer. In patients with stage III rectal cancer, the rates were 58.8% and 46.0% in the laparoscopic-surgery group and open surgery-group (difference, 12.8 percentage points; 95% CI, 2.0 to 23.6).

Table 2. Involved circumferential resection margin and locoregional recurrence at 5 years postoperatively

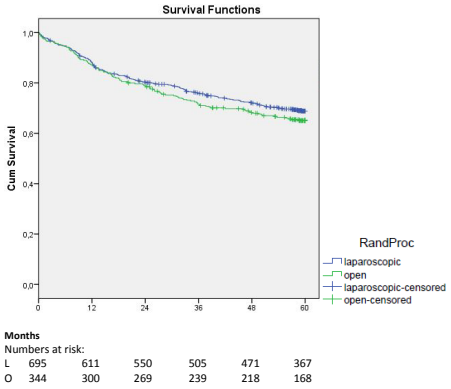
Type of Lesion and Surgery	Involved Circumferential Resection Margin*		Locoregional Recurrence in Intention-to-Treat Population		Locoregional Recurrence in As-Treated Population	
	Patients with Finding†	Between-Group Difference‡	Rate	Between-Group Difference‡	Rate	Between-Group Difference‡
	no./total no. (%)	*percentage points (95% CI)*	*%*	*percentage points (90% CI)*	*%*	*percentage points (90% CI)*
All lesions						
Laparoscopic surgery	56/588 (10)	-0.5 (-4.9 to 3.5)	6.4	-0.5 (-4.0 to 3.0)	5.7	-2.5 (-6.1 to 1.1)
Open surgery	30/300 (10)		6.9		8.2	
Upper rectal lesion						
Laparoscopic surgery	18/196 (9)	-0.1 (-8.2 to 6.4)	4.0	0 (-4.8 to 4.8)	3.5	-1.5 (-6.5 to 3.5)
Open surgery	9/97 (9)		4.0		5.0	
Middle rectal lesion						
Laparoscopic surgery	22/228 (10)	6.2 (0.1 to 11.2)	7.7	3.1 (-2.2 to 8.4)	6.9	0.6 (-5.1 to 6.3)
Open surgery	4/115 (3)		4.6		6.3	
Lower rectal lesion						
Laparoscopic surgery	15/164 (9)	-12.4 (-23.2 to -3.0)	7.0	-7.1 (-15.9 to 1.7)	6.5	-8.6 (-17.3 to 0.1)
Open surgery	17/79 (22)		14.1		15.1	

* An involved circumferential resection margin was defined as the presence of tumor cells within 2 mm of the lateral surface of the mesorectum. This finding is a risk factor for locoregional recurrence (i.e., recurrence in the pelvic or perineal area).

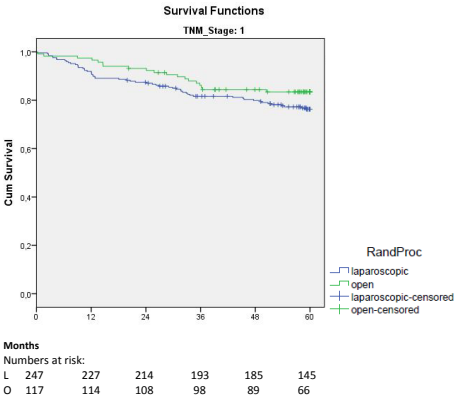
† The denominator for the percentage calculation in this category was the number of patients without complete remission.

‡ Between-group differences were calculated by subtracting the percentage of patients with the finding in the open-surgery group from the percentage in the laparoscopic-surgery group.

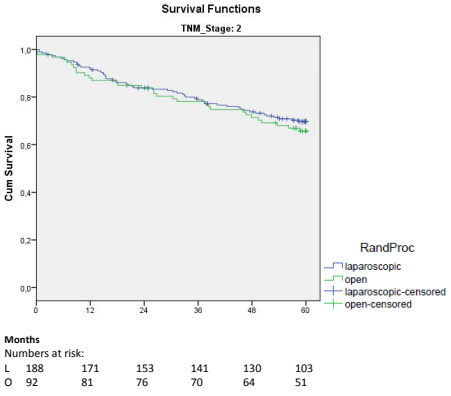
Figure 2. Disease-free survival



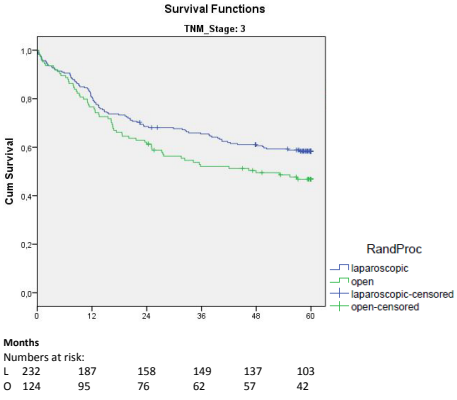
a. All stages



b. Stage I

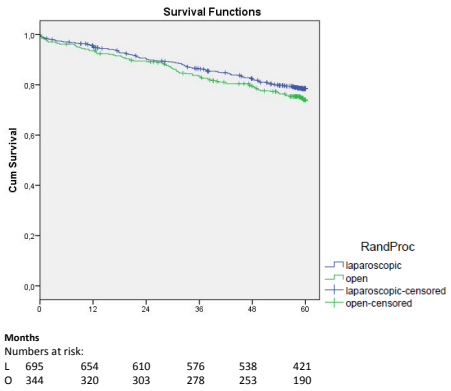


c. Stage II

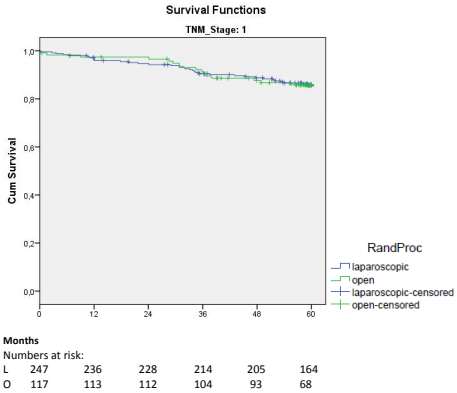


d. Stage III

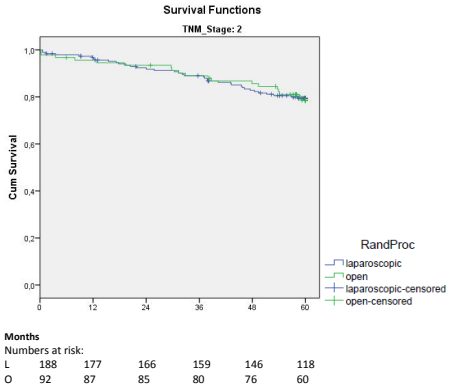
Figure 3. Overall survival



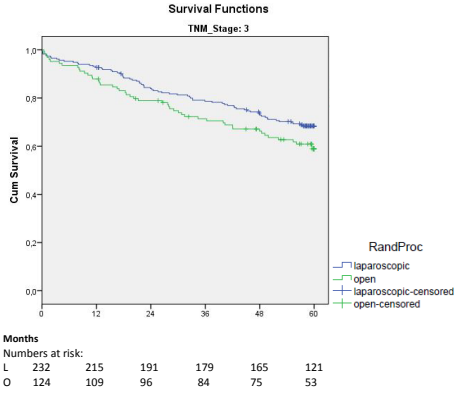
a. All stages



b. Stage I



c. Stage II



d. Stage III

Overall survival

At 5 years follow-up, 230 patients had died and the overall survival rates were 78.5% in the laparoscopic-surgery group and 74.0% in the open surgery group (difference, 4.5 percentage points; 95% CI, -1.2 to 10.2). In patients with stage I, II or III rectal cancer, no significant differences were found between the two treatment groups (Figure 3).

In as-treated analysis, overall survival rates were 78.9% in the laparoscopic-surgery group and 73.2% in the open-surgery group (difference, 5.7 percentage points; 95% CI, 0.1 to 11.4). In patients with stage I, II or III rectal cancer, no significant differences were found between the two treatment groups.

Discussion

Surviving is the main goal on the mind of patients diagnosed with rectal cancer. Even though improved short-term outcomes after laparoscopic surgery compared to open surgery were reported, survival after laparoscopic surgery is of more importance to these patients.

This study shows similar overall survival rates 5 years after either laparoscopic or open surgery. However, in as-treated analysis laparoscopic surgery resulted in improved overall survival at 5 years after surgery. A significant difference of 5.7% was found in favor of patients that were operated laparoscopically. Twelve patients changed their initially assigned treatment group. Five patients randomized to the open-surgery group were operated laparoscopically (three of them requested laparoscopic surgery after randomization, in the other two the reason was unknown). Seven patients assigned to the laparoscopic-surgery group underwent open surgery (one because of poor pulmonary condition, in five cases there was no laparoscopic surgeon available and for one patient the reason was unknown). Because reasons for change in treatment group were not associated with clinical or tumor characteristics (except for the patient with poor pulmonary function), we feel the results of the as-treated analysis should not be ignored.

Previously, we reported at 3 years follow-up similar survival rates for laparoscopic and open surgery.[3] However, a difference of almost 13% in disease-free survival was observed in patients with stage III disease in favor of the laparoscopic group. At 5 years after either laparoscopic or open resection disease-free survival rates were 68.8% and 64.8%, respectively. Interestingly, the difference in disease-free survival in patients with stage III rectal cancer remained apparent in favor of laparoscopic surgery, supporting the hypothesis that less surgical trauma reduces tumor recurrence and is associated with reduced stress response and therefore improved immune function.[14,15]

Rectal cancer treatment has improved significantly over the past centuries. With the use of multimodal therapies, including (chemo)radiotherapy and surgery, patients have a better prognosis with higher chance on survival. Two hundred years ago 1 out of 5 operated patients died during their surgery and patients that did survive had a risk of 80% to develop locoregional recurrence.[16,17] This study shows that 7-8 out of 10 patients survived their cancer 5 years after either laparoscopic or open surgery with no significant difference between laparoscopic and open surgery. Other trials such as the Comparison of Open versus laparoscopic surgery for mid and low REctal cancer After Neoadjuvant chemoradiotherapy (COREAN) trial reported also at least similar survival outcomes between laparoscopy and open surgery in patients with rectal cancer.[1]

One of the other main concerns for patients with rectal cancer is the risk of development of recurrence of cancer in the pelvic or perineal area (locoregional recurrence). This serious condition is associated with intractable pain and compromises the quality of life. Our study shows that most of the locoregional recurrences develop within 3 years after surgery. The previously reported locoregional recurrence rate at 3 years was 5% in both treatment groups, accounting for 46 recurrences in total. At 5 years postoperatively in 13 patients new locoregional recurrences were reported and again similar rates were observed after laparoscopic and open resection. In patients with low rectal cancer, laparoscopic resection was associated with a lower rate of involved circumferential resection margins and subsequently at 3 years postoperatively a lower locoregional recurrence rate compared to open resection (4.4% vs. 11.7%, respectively). The results at 5-year follow-up show the same phenomenon and a similar difference in locoregional recurrence rate of 7% was found between the laparoscopic and open group. Large trials reporting on 5-year outcomes after rectal cancer surgery are scarce. In the Dutch Total Mesorectal Excision trial the locoregional recurrence rate was 5.6% at 5 years after open surgery for rectal cancer, combined with preoperative radiotherapy, and 10.9% when surgery alone was performed.[18] The Conventional versus Laparoscopic-Assisted Surgery in Colorectal Cancer (CLASICC) trial reported rates of 9.4% in the laparoscopic group and 7.6% in the open group in patients after anterior resection.[2] Data for abdominoperineal resection were not shown, however no difference was found between the two groups. Another randomized study conducted by Lujan et al. showed locoregional recurrence rates of 4.8% and 5.3% at 5 years after laparoscopic and open resection, respectively.[19] These rates are all comparable to the rates of the COLOR II trial. Data from the COREAN study group at 3 years postoperatively showed a lower locoregional recurrence rate after laparoscopic resection compared with the COLOR II trial (2.6% vs. 5.0%).[1] However, follow-up data at 5 years are to be awaited.

In two recently published large randomized trials, noninferiority of laparoscopic surgery for rectal cancer compared with open surgery could not be established regarding a composite primary endpoint of circumferential resection margin, completeness of specimen and distal resection margin. In the American College of Surgeons Oncology Group (ACOSOG) Z6051 study conducted in the USA and Canada, 462 patients with stage II or III rectal cancer were included between 2008 and 2013.[10] The primary endpoint, rate of successful resection, was 81.7% in the laparoscopic-surgery group and 86.9% in the open-surgery group, not supporting noninferiority (difference, -5.3 percentage points; 95% CI, -10.8 to ∞). Involvement of the circumferential resection margin was observed in 12.1% of the patients in the laparoscopic-surgery group and in 7.7% in the open-surgery group. From Australia and New Zealand, the Australasian Laparoscopic Cancer of the Rectum Trial (ALaCaRT) trial included 402 patients

randomized between 2010 and 2014 with T1-T3 rectal adenocarcinoma.[11] The primary endpoint was similar to the ACOSOG Z6051 study. In the laparoscopic-surgery group, the rate of successful resection was 82.0%, compared to a 89.0% rate in the open-surgery group. These results did also not support noninferiority for laparoscopic resection of rectal cancer (difference, -7.0 percentage points; 95% CI,-12.4 to ∞). The rate of involvement of circumferential resection margin was 7.0% in the laparoscopic-surgery group and 3.0% in the open-surgery group. Both trials concluded that there was not sufficient evidence for the routine use of laparoscopic surgery. As reported in literature, involvement of circumferential resection margin is a strong predictor for locoregional recurrence.[20] However, it has been shown that there is no direct correlation between these two factors. In the first multicenter randomized trial evaluating the effect of laparoscopic surgery in rectal cancer (the CLASICC trial), a higher rate of involved circumferential resection margin was found in patients after laparoscopic resection of rectal cancer (12%) compared to open resection (6%). However, this difference did not translate into higher locoregional recurrence rates in patients after laparoscopic surgery 3 years after surgery.[2] Therefore, the effect of the involved circumferential resection margin on locoregional recurrence in the ACOSOG Z6051 and ALaCaRT trials has to be awaited in order to make definitive recommendations.

In the ACOSOG Z6051 and ALaCaRT trials the conversion rates are relatively low (11.3% and 9%, respectively),[10,11] suggesting that there is no effect of a learning curve and that surgeons enrolled in the study were credentialed. Nevertheless, details regarding if these rates were stable over time are lacking. Moreover, the very wide confidence intervals of both trials could indicate that the laparoscopic technique was not completely standardized. Furthermore, in the ACOSOG Z6051 trial more than 90% of the patients received neoadjuvant therapy and in the ALaCaRT trial it was reported that half of the patients were treated with preoperative radiotherapy. In the COLOR II trial, neoadjuvant chemotherapy was administered in one third of patients, and neoadjuvant radiotherapy in almost two third of the patients in both treatment groups. Due to differences in neoadjuvant therapy, as well as disparities in included T-stages and considerations of involvement of circumferential resection (margin of 1 mm vs. 2 mm) comparison of the ACOSOG Z6051, ALaCaRT and COLOR II should be interpreted with caution.

A limitation of this study is that in contrast to clinical examination, imaging of chest, abdomen and pelvis was not mandatory at 5 years follow-up. Therefore, recurrent disease could be missed if patients were free of any symptoms and clinical examination did not reveal signs of recurrence.

In conclusion, 5-year outcomes of the COLOR II trial support the evidence that laparoscopic and open surgery in patients with noninvasive and nonmetastatic rectal cancer result in similar survival and recurrence rates. In as-treated analysis improved overall survival was observed in patients after laparoscopic surgery.

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CHAPTER 6

Conversions in laparoscopic surgery for rectal cancer

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Abstract

Background Laparoscopic surgery offers patients with rectal cancer short-term benefits and similar survival rates as open surgery. However, selecting patients who are suitable candidates for laparoscopic surgery is essential to prevent intra-operative conversion from laparoscopic to open surgery. Clinical and pathology variables were studied among patients who had converted laparoscopic surgeries within the COLOR II trial to improve patient selection for laparoscopic rectal cancer surgery.

Methods Between January 20, 2004 and May 4, 2010, 1044 patients with rectal cancer enrolled in the COLOR II trial and were randomized to either laparoscopic or open surgery. Of 693 patients who had laparoscopic surgery, 114 (16%) were converted to open surgery. Predictive factors were studied using multivariate analyses and morbidity and mortality rates were determined.

Results Factors correlating with conversion were: age above 65 years (OR 1.9; 95% CI 1.2-3.0: p=0.003), BMI greater than 25 (OR 2.7; 95% CI 1.7-4.3: p<0.001) and tumor location more than 5 cm from the anal verge (OR 0.5; CI 0.3-0.9). Gender was not significantly related with conversion (p=0.14). In the converted group, blood loss was greater (p<0.001) and operating time was longer (p=0.028) compared with the non-converted laparoscopies. Hospital stay did not differ (p=0.06). Converted procedures were followed by more postoperative complications compared with laparoscopic or open surgery (p=0.041 and p=0.042, respectively). Mortality was similar in the laparoscopic and converted groups.

Conclusions Age above 65 years, BMI greater than 25 and tumor location between 5 and 15 cm from the anal verge were risk factors for conversion of laparoscopic to open surgery in patients with rectal cancer.

Introduction

Laparoscopic surgery for colon cancer is oncologically safe and associated with improved postoperative recovery.[1-4] Evidence supporting laparoscopic surgery in patients with rectal cancer has been provided by two large randomized trials, the Comparison of open versus laparoscopic surgery for mid and low rectal cancer after neoadjuvant chemoradiotherapy (COREAN) trial[5] and the Colorectal cancer laparoscopic or open resection (COLOR) II trial.[6,7] However, two recently published randomized controlled trials failed to establish noninferiority of laparoscopic surgery for rectal cancer using pathologic oncologic markers.[8,9] In the COLOR II trial in more than 1,000 patients, the rates of locoregional recurrences at 3 years after index surgery were similar, 5.0% in the laparoscopic and in the open group (90% CI, -2.6 to 2.6).[7] In one out of six patients who had laparoscopic surgery in this trial, laparoscopy was converted to open surgery. Although conversions in laparoscopic surgery should not be considered as failures, prevention of conversions is important because inferior short-term outcomes in rectal cancer patients after conversion from laparoscopic to open resection have been reported.[10,11] The aims of this study were to identify risk factors for conversion and to report the early outcomes of converted laparoscopic surgeries in patients with rectal cancer.

Patients and methods

The COLOR II trial is an international multicenter randomized controlled trial comparing curative laparoscopic surgery with conventional open surgery for rectal cancer. This trial is registered as clinical trials Identifier NCT00297791. In order to participate in the COLOR II trial surgeons had to submit unedited recordings of 5 consecutive cases of laparoscopic total mesorectal excision (TME) along with associated pathology reports. A more detailed description of the study design and methods has been published previously.[12] Patients with solitary rectal cancer, staged as cT1, cT2 or cT3 tumors suitable for curative resection, were eligible for inclusion in the trial. A laparoscopic procedure was defined as converted to open surgery when dissection of the mesorectum was not completed laparoscopically. Utilizing the extraction site for open transection of the distal rectum was not considered a conversion. Analyses included determination of patient-related possible risk factors such as gender, age, previous abdominal surgery, American Society of Anesthesiologists (ASA) classification and body mass index (BMI). Other possible risk factors or mediators such as location of the tumor (upper rectum 10-15 cm from the anal verge, middle rectum 5-10 cm, or lower rectum 0-5 cm), diameter of the tumor, clinical T-stage (cT-stage), preoperative radiotherapy or chemoradiotherapy were included in the analyses. Comparisons between the open surgery group, the converted group and the laparoscopic group were performed regarding blood loss, operating time, postoperative complications, length of hospital stay, radicality of resection and mortality.

Statistical analysis

Statistical analysis was performed using the SPSS software package (SPSS 20.00 for Windows; IBM). Means, standard deviations, medians, interquartile ranges and percentages were computed separately for the open, completed laparoscopic and converted group. The influence of risk factors for conversion was examined using cross tabulations and logistic regression models. We examined patient characteristics (age, gender, BMI, ASA classification), tumor characteristics (diameter, position, location, cT-stage) and preoperative treatment modalities (radiotherapy and chemoradiotherapy). Numeric data were categorized for application in logistic regression models. The outcomes of the converted group were compared to the outcomes of the laparoscopic and open groups using cross tabulations and Chi square tests or exact tests where necessary and One-Way-Anova plus post hoc analyses with Bonferroni corrections. A P-value <0.05 was considered significant.

Results

In the COLOR II trial 699 patients had been randomized to laparoscopic surgery. Twelve patients were not operated according to randomization; seven patients randomized for laparoscopic surgery had open surgery and five patients randomized to open surgery underwent laparoscopic surgery. Data concerning conversion were missing in four patients. One hundred fourteen patients (16%) had their laparoscopic surgeries converted to open surgery. In male patients, 80/441 (18%) operations were converted versus 34/252 (13%) in female patients. In 22% (25 patients, 24 male and 1 female) of all converted patients a small pelvis was noted by the surgeon as reason for conversion. Baseline characteristics of all patients included for analysis in the COLOR II trial are shown in Table 1. The conversion rates at the start and the end of trial were comparable (Figure 1). In patients with high rectal cancer, total mesorectal excision (TME) was performed in 241 (71%) patients, partial mesorectal excision (PME) in 90 (27%) and abdominoperineal resection (APR) in 7 (2%) patients. For patients with cancer in the middle rectum, TME was performed in 340 (84%), APR in 48 (12%) and PME in 15 (4%) patients. In patients with rectal carcinoma within 5 cm from the anal verge, an APR was performed in 225 (77%) cases, in 67 cases (23%) a TME was performed and 2 patients (<1%) underwent PME.[6] 30% of the patients in the laparoscopic group versus 37% of the patients in the converted group (p=0.119) had a diverting ileostomy.

Figure 1. Conversion per year of the COLOR II trial

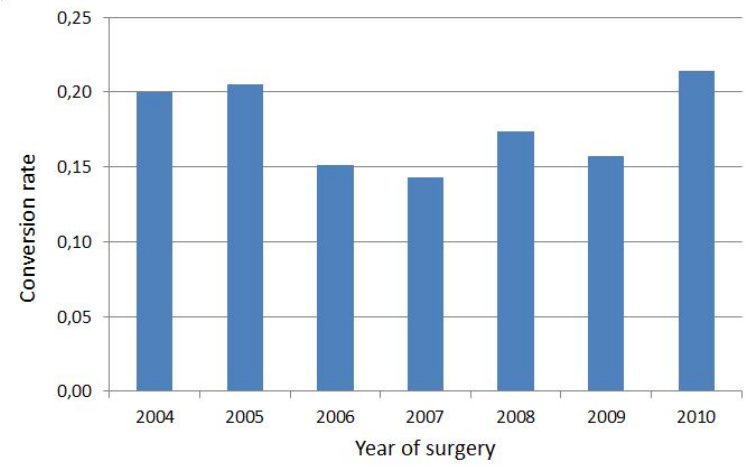

Table 1. Baseline characteristics, *Numbers and percentages or median and interquartile range*

	Laparoscopic group	Open group	Conversion group
Gender (p=0.049)			
Male	361/579 (62%)	215/347 (62%)	80/114 (70%)
Female	218/579 (38%)	132/347 (38%)	34/114 (30%)
Age (years) (p=0.852)	67.0 [59.0-74.0]	67.0 [58.0-74.0]	70.0 [63.8-75.5]
Body-mass Index (kg/m^2) (p=0.587)	25.5 [23.4-28.3]	25.7 [23.2-28.4]	26.1 [23.6-28.0]
American Society of Anesthesiologists category (p=0.689)			
I	134/568 (23.6%)	68/343 (19.8%)	21/111 (18.9%)
II	323/568 (56.9%)	212/343(61.8%)	66/111(59.5%)
III	107/568 (18.8%)	62/343 (18.1%)	23/111 (20.7%)
IV	4/568 (0.7%)	1/343 (0.3%)	1/111 (0.9%)
Missing data	11/579 (1.9%)	4/347 (1.2%)	3/114 (2.6%)
Preoperative radiotherapy (p=0.938)	339/579 (59%)	200/347 (58%)	68/114 (60%)
Preoperative chemotherapy (p=0.251)	166/498 (33%)	101/299 (34%)	27/106 (25%)
Missing	81/579 (14%)	48/347 (14%)	8/114 (7%)
Abdominal surgery in history (p=0.665)	150/538 (28%)	90/330 (27%)	35/109 (32%)
Missing	41/579 (7%)	17/347 (5%)	5/114 (4%)
Tumor location (p=0.90)			
High rectum	181/579 (31%)	116/347 (33%)	41/114 (36%)
Medium rectum	218/579 (38%)	137/347 (39%)	52/114 (46%)
Low rectum	180/579 (31%)	94/347 (27%)	21/114 (18%)

Patient-related factors

There were 80 males and 34 females in the converted group. Analysis of gender did not show a significant difference in converted surgeries between male and female (p=0.109). Median age in the laparoscopic non-conversion group was 67 years [IQR 59.0-74.0], whereas for the converted group this was 70 years [IQR 63.8-75.5]. Age above 65 years increased the risk of intraoperative conversion (OR 1.9; CI 1.2-3.0). Median BMI for the group of non-converted patients was 25.2 [IQR 23.1-27.8] and for converted patients 26.6 [IQR 25.0-30.5]. BMI above 25 increased the risk of intraoperative conversion (OR 2.7; CI 1.7-4.3) (Table 2). Other patient-related factors, such as previous abdominal surgery, ASA-classification, were not independently related to the risk of conversion. Reasons for intraoperative conversion as documented by the surgeon are shown in Table 2.

Table 2. Reasons for intraoperative conversion as documented by surgeon

Reasons for conversion as documented by surgeon	Conversions n/n total (%)
Narrow pelvis	25/114 (22)
Extensive adhesions	14/114 (12)
Obesity	11/114 (10)
Fixation of the tumour	10/114 (9)
Technical	7/114 (6)
Anatomical difficulties	7/114 (6)
Poor vision	6/114 (5)
Bleeding	6/114 (5)
Large tumor	5/114 (4)
Injury to ureter	2/114 (2)
Other reason	17/114 (15)
Missing data	4/114 (4)

Tumor-related factors

When used as reference group, laparoscopic surgeries in patients with low rectal tumors were less likely to be converted as compared to patients with cancer in the middle or upper rectum (OR 0.5; CI 0.3-0.9). Forty-one of 222 (18.5%) patients with an upper rectal tumor were converted and 52 of 270 (19.3%) patients with cancer in the middle rectum were converted (Table 3). For patients with cancer in the lower rectum, conversion occurred in 10.4% (21/201). Previous chemoradiotherapy was not a risk factor for conversion nor was cT-stage (p=0.586). The rate of involved circumferential margins, defined as presence of malignant cells within 2 mm of the circumferential margin and the outermost part of the tumor, was 9% (45/499) in patients who had completed laparoscopic rectal cancer surgery while this rate was 9.6% (10/104) in patients who had converted procedures (p=0.847). More detailed data about tumor-related outcomes for each group (laparoscopic, open, and converted) are shown in Table 4.

Table 3. Odds ratio's for conversion (n = 693)

Characteristics	Number	Odds ratio	95% confidence interval of odds ratio	
Age above 65 years	394	1.9	1.2	3.0
Age 65 years and below	299	Reference		
Male	441	1.4	0.9	2.2
Female	252	Reference		
BMI > 25	384	2.7	1.7	4.3
BMI no data available	15	1.4	0.3	6.7
BMI ≤25	294	Reference		
Tumor location (10-15 cm)	222	2.0	1.1	3.5
Tumor location (5-10 cm)	269	2.1	1.2	3.7
Tumor location (0-5 cm)	202	Reference		

Table 4. Tumor related data, ***Numbers and percentages or median and interquartile range, *patients with complete remission were left out the analysis***

	Laparoscopic group	Open group	Conversion group
Tumor related data			
Completeness of resection	488/552 (88%)	305/339 (90%)	97/110 (88%)
Missing data	27/579 (5%)	8/347 (2%)	4/114(4%)
Positive CRM	45/499 (9%)	31/308 (10%)	10/104 (10%)
Missing data	80/ (14%)	39/347 (11%)	10/114 (9%)
Median distance to distal resection margin (cm)*	3.0 [2.0-4.5]	3.0 [1.8-5.0]	3.0 [1.5-5.0]
Missing data	33/349 (6%)	17/328 (5%)	12/111 (11%)
Number of lymph nodes harvested	13 [9-17]	14 [10-19]	16 [12-20]
Missing data	20/579 (2%)	4/347 (1%)	4/114 (4%)

Analysis after exclusion of APR procedures

A subanalysis of risk factors for conversion was performed including only patients who underwent a sphincter saving procedure (APR procedures were excluded). A total of 197 APR procedures was excluded (153/199 laparoscopic procedures in the lower rectal tumor group, 38/266 in the middle rectal cancer group, and 6/223 in the high rectal cancer group), leaving 491 patients with sphincter saving procedures for analysis (data was missing in 9 patients). Risk factors for conversion were age above 65 years (OR 2.7; CI 1.5-4.7) and BMI greater than 25 (OR 2.3; CI 1.3-4.0). The conversion rate in patients with low tumors in this subgroup was 17.4%, for middle and high rectal tumors this was 19.7% and 18%, respectively (p=0.866). Tumor location was not associated with increased risk of conversion in this subgroup of patients. Other studied factors such as previous abdominal surgery, gender, ASA-classification, previous chemoradiotherapy and cT-stage did not show to be predictive factors for conversion for this subgroup of patients.

Converted laparoscopic surgery vs completed laparoscopic surgery

Median operating time was significantly longer in the converted group compared to the completed laparoscopic surgery group; 256 minutes vs 233 minutes (p=0.028). Patients had more blood loss during converted surgery than during completed laparoscopic surgery; 450 mL vs 150 mL (p<0.001). Return of bowel function measured by first passage of stool and oral tolerance of 1 Liter of fluid occurred earlier after laparoscopic surgery compared to the patients who had their surgery converted (p<0.001 and p=0.015, respectively). Also the number of patients with at least one postoperative complication was smaller after laparoscopic surgery than after conversion (p=0.041). Length of hospital stay (p=0.063) and mortality rate within 28 days after index surgery (p=0.512) was similar in both groups (Table 5).

Table 5. Operative and postoperative outcomes: converted to open surgery vs laparoscopic and open surgery (p-value reflects outcomes compared to outcomes of the converted group of patients)

Variable	Converted to open surgery	Laparoscopic surgery	Open Surgery
Median blood loss in mL [IQR]	450 [300-750]	150 [100-300] (p<0.001)	400 [200-700] (p=0.664)
Median skin to skin time in min. [IQR]	256 [180-337]	233 [184-291] (p=0.028)	190 [151-240] (p=0.013)
Median hospital stay in days [IQR]	11.0 [8-15]	8.0 [6-13] (p=0.063)	9.0 [7-12] (p=0.126)
Median days until first bowel movement [IQR]	3.0 [2-5]	2.0 [1-3] (p<0.001)	3.0 [2-5] (0.900)
Median days until oral tolerance of 1 liter fluids [IQR]	2.0 [1-4]	1.0 [1-2] (p=0.015)	2.0 [1-3] (p=0.230)
Any postoperative complication (percentage)	55/114 (48%)	220/579 (38%) (p=0.041)	130/347 (37%) (p=0.042)
Abscesses	11/114 (7%)	41/579 (7%) (p=0.341)	21/347 (6%) (p=0.190)
Ileus	6/114 (5%)	28/579 (5%) (p=0.847)	11/347 (3%) (p=0.304)
Cardiac	6/114 (2%)	12/579 (2%) (p=0.050)	10/347 (3%) (p=0.228)
Respiratory	4/114 (4%)	15/579 (3%) (p=0.583)	11/347 (3%) (p=0.860)
Death within 28 days (percentage)	2/114 (2%)	6/579 (1%) (p=0.512)	6/351 (2%) (p=0.377)

Converted laparoscopic surgery vs open surgery

The operating times were significantly longer in the converted group compared with open surgery, 256 minutes [IQR 180-337] vs 190 minutes [IQR 151-240], respectively (p=0.013). Median blood loss was comparable, 450 mL and 400 mL for the conversion group and open group, respectively. At least one postoperative complication occurred in 55 out of 114 patients (48%) in the converted group; after primary open surgery this was 37% (130/347), p=0.042. Length of hospital stay (p=0.126) and mortality within 28 days were comparable between the converted and open surgery groups (Table 5).

Discussion

Patients with rectal cancers located more than 5 cm cranially from the anal verge, patients with BMI above 25 and patients with age above 65 years had a higher risk of conversion in this randomized trial of laparoscopic versus open surgery for rectal cancer.

In patients with low rectal cancer, defined as tumors located within 5 cm from the anal verge, the conversion rate from laparoscopic to open surgery was significantly lower than in patients with middle or high rectal tumors. In part this could be explained by the fact that more than three-quarters (76.9%) of patients with a tumor below 5 cm from the anal verge underwent an APR. Subanalysis excluding APR procedures showed similar conversion rates in patients with high, middle and low rectal tumors and tumors located 5-15 cm from the anal verge were not associated with increased risk of conversion in this subgroup of patients. In tumors located in the low and middle rectum, a complete TME has to be performed in order to achieve a radical resection and lower the risk of recurrence. One of the most difficult parts in TME is the distal dissection of the rectum because the narrow pelvis restricts maneuvering of surgical devices. This could compromise a tumor free resection margin. In patients with low rectal cancers undergoing APR, the distal part of the dissection is commonly done through the perineal approach. Hence, these APR procedures are not completely laparoscopic resections, but rather composite procedures.

The APR rate in patients with low rectal cancer in the COLOR II trial (77%) is in accordance with a Scandinavian study evaluating oncological outcomes after TME for cancer of the lower rectum. This study group reported an APR rate of 85% in patients with a tumor within 5 cm from the anal verge.[13] Other trials such as the COREAN[5] and CLASICC[3] trial showed an APR rate of 11.2% and 25%, respectively. However our data on APR rates are difficult to comparable to these trials, because in these trials rates were not reported based on tumor height but for the entire study population. The ACOSOG Z6051 trial showed an APR rate of 25.4% in the laparoscopic group. In this trial surgeons performed a coloanal anastomosis whenever possible. In our trial there were only a few cases of coloanal anastomosis because this technique was not favorable for many of the participating surgeons. To overcome the problem of high APR rates in low rectal cancer, the new Transanal Total Mesorectal Excision (TaTME) technique has been developed. In TaTME the tumor is approached transanally, facilitating precise dissection of the mesorectum and allowing creation of a low anastomosis.[14-16]

Furthermore, this study showed that BMI above 25 was associated with a higher conversion rate. An explanation for this finding is that the mesorectum in obese patients will further

reduce the already narrow pelvic space causing limited working space. However, it is reported that laparoscopic colorectal cancer surgery is safe in obese patients in terms of postoperative morbidity, harvested lymph nodes and radical resection margins and offers this group of patients similar short-term benefits as non-obese patients.[17]

In our study, age above 65 years was also an independent risk factor for conversion to open surgery in patients with rectal cancer. Data from large national databases on more than 43,000 laparoscopic cholecystectomies and more than 33,000 appendectomies, have shown older age to be a risk factor for conversion after laparoscopic cholecystectomy and appendicectomy.[18,19] These higher rates were related to more comorbidities in the elderly, based on the Charlson co-morbidity index. Tekkis and colleagues showed an increased conversion rate in older patients after analyzing clinical data from 1253 patients undergoing laparoscopic colorectal surgery.[20] In our trial, previous abdominal surgeries were not reported more often in the group of patients with age over 65 years compared to the group of patients with age below 65 years. Others have reported significant benefits from laparoscopic surgery in older patients such as less postoperative pneumonia and cardiac complications.[21] The exact impact and explanation of age as risk factor for conversion from laparoscopic rectal cancer surgery to open surgery remains unclear. More studies are needed to assess age as a risk factor for conversion to open surgery in laparoscopic rectal cancer surgery.

Several studies identified male gender as risk factor for conversion.[22-24] However, in our study male gender was not significantly associated with a higher risk of conversion compared with females. A 'narrow pelvis' was the reported reason for conversion in 22% of patients (25 patients) and of these patients only 1 patient was female. These data might reflect that laparoscopic surgery in male patients with a narrow pelvis could be more demanding resulting in a higher risk of conversion. Significantly shorter pelvic in- and outlets and greater depth in males compared with females are reported, but not as risk factor for conversion.[25,26] Using gender as substitute for pelvic size is not an accurate method and actual measurements should be provided. In our study we did not collect objective data concerning the diameter of the pelvis of each patient. A study evaluating pelvic measurements showed that anterioposterior diameter of the pelvis at the tumor level was a predictive factor for conversion, but only in females.[27] Precise preoperative assessment of the size of the pelvic space could improve selection of patients for laparoscopic rectal cancer surgery.

The debate regarding a clear definition of conversion continues. In 2008 Shawski and colleagues published the results of a web-based survey conducted among colorectal surgeons on

the definition of conversion in laparoscopic colorectal surgery.[28] Their conclusion was that any incision made earlier than planned was considered conversion. In the COLOR II trial, a laparoscopic procedure was judged converted to open surgery if the dissection of the mesorectum was not completed laparoscopically. However, utilizing the extraction site for open insertion of a stapler to transect the distal rectum was not considered a conversion. Most studies do not define conversion and several reports of case series use a definition based on the length of incision, ranging from an incision >5 cm to >10 cm.[28] In a recently published Delphi study multidisciplinary consensus for the definition of conversion was achieved differentiating between strategic and reactive conversion.[29] Strategic conversion was defined as "a standard laparotomy that is made directly after the assessment of the feasibility of completing the procedure laparoscopically and because of anticipated operative difficulty or logistic considerations". Reactive conversion was defined as "the need for a laparotomy because of a complication or (extension of an incision) because of (anticipated) operative difficulty after a considerable amount of dissection (i.e., >15 min in time)". The latter has shown to be associated with increased postoperative morbidity compared with strategic conversion.[30] In the COLOR II trial such distinction was not made. Future reports addressing conversion in laparoscopic surgery should use the definition as stated in the mentioned Delphi study,[29] differentiating between strategic and reactive conversion. Only then proper assessment of the feasibility of a surgical procedure can be made.

The level of surgeon's experience is believed to be an important factor influencing conversion rate.[31] This was reported in the CLASICC trial reflected by a reduction of conversion rate during the recruitment period of the trial from 38% in the first year to 16% in the last year.[32] However, conversion rates at the start of the COLOR II trial were comparable with the conversion rates at the end of the trial. This finding is possibly due to only allowing those surgeons that submitted recordings of five consecutive laparoscopic procedures for evaluation and completeness of the specimen of these procedures was confirmed by the pathologist. The recently published ACOSOG Z6051 and ALaCaRT trials reported conversion rates of 11% and 9%, respectively.[8,9] However, the ACOSOG Z6051 and ALaCaRT trials were conducted between 2008-2013 and 2010-2014 versus the COLOR II trial from 2004-2010. Improved surgical technology may have contributed to the low conversion rates in these more recently conducted trials.

In the Netherlands there has been a remarkable increase of laparoscopic procedures performed for rectal cancer during the last years. Five years ago only 37% of the rectal cancer patients had laparoscopic surgery and a conversion rate of 14% was reported. During the

years 2011, 2012 and 2013 laparoscopy was used in 45%, 58% and 70% of the rectal cancer surgeries, respectively. Recently the Dutch Surgical Colorectal Audit (DSCA) published the annual report of 2014 showing that 75% of the rectal cancer patients that were operated last year underwent laparoscopic resection. Moreover, the conversion rate reported for 2014 was 10.6%.[33] It has been suggested that the conversion rate can be reduced to 4% when more than 150 laparoscopic colorectal procedures have been performed by one surgeon.[34] Supervised training in laparoscopic surgery is shown to be effective without compromising the outcomes for the patients subject to these supervised procedures.[35-37]

In conclusion, in our study patients with rectal cancer located more than 5 cm from the anal verge, BMI greater than 25 or age above 65 years have a higher risk of conversion. Therefore, awareness is important in these patients in whom a laparoscopic approach is considered.

Author disclosures

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PART II

THE FUTURE: COLOR III

CHAPTER 7

Transanal total mesorectal excision for rectal carcinoma: short-term outcomes and experience after 80 cases

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Abstract

Background Low anterior resection for distal and mid-rectal cancer is associated with high positive resection margins. Transanal total mesorectal excision (TaTME) is a new treatment in which the rectum is dissected transanally according to TME principles. The short-term results and oncological follow-up of the first 80 patients were described.

Methods Between June 2012 and September 2014, all patients in the Gelderse Vallei Hospital and the VU University Medical Center with histologically proven distal or mid-rectal carcinomas without evidence of distant metastases underwent TaTME. Patients with T4 tumors were excluded. Transanal mobilization was performed with the aid of a single port and endoscopic instruments according to TME criteria.

Results Eighty patients were operated in a period of 2 years. Laparotomy was recommended and performed in four patients. Postoperative morbidity was 39%. Ten (12%) complications were graded as severe (Clavien-Dindo grade 3, 4 and 5) and needed re-intervention. Median operative time was 204 min (range 91-447). Median hospital stay was 8 days (range 3-41). Specimens were graded as complete in 88% of the patients, nearly complete in 9% and incomplete in 3%. A positive circumferential resection margin (<2 mm) was observed in two patients. During the two and half years study period, a local recurrence was observed in two patients.

Conclusion TaTME is a safe alternative to standard laparoscopic TME in selected low-risk patients with rectal carcinoma when treated by an experienced colorectal team. In the future, randomized trials are necessary to prove its oncological safety.

Rectal cancer management and rectal cancer surgery are in progress, and new techniques aiming for better functional results and better oncological outcomes are being developed. Ever since Heald et al. stressed the importance of the quality of surgery in reducing the number of local recurrences, a significant reduction in the local recurrence rate has been achieved.[1,2]

Results from the Dutch TME trial further stressed the importance of the technical quality. [3,4] Increased risk of local tumor recurrence has been reported for patients who underwent a potentially curative procedure, but had an incomplete or damaged specimen.[5]

Even though progress has been made, total mesorectal excision (TME) surgery can still be improved. Bondeven et al.[6] evaluated the completeness of the mesorectal excision by postoperative magnetic resonance imaging (MRI) and showed residual mesorectum in 36% of patients who should have had complete excision based on the height of the tumor. Furthermore, low anterior resections for mid- and distal rectal cancer are associated with relatively high circumferential margin involvement. Laparoscopic techniques were expected to improve the quality of surgery, by improving visualization of the pelvic cavity and therefore facilitating mobilization of the rectum. However, until now, evidence for oncological superiority is lacking.[7]

Transanal TME (TaTME) is a new treatment option, which is expected to revolutionize the surgical treatment of rectal cancer. During TaTME, the rectum is dissected transanally according to TME principles with the use of endoscopic instruments, the so-called down-to-up TME. An important advantage of this new technique is that a sufficient distal margin can be obtained under direct vision. Furthermore, the parts that are often considered the most difficult of the standard laparoscopic TME, the part ventral to the rectum and the most distal dorsal part, are much better visualized.

In this article, we describe our initial experience with the TaTME and report oncological follow-up.

Materials and methods

Between June 2012 and September 2014, all patients in the Gelderse Vallei Hospital and the VU University Medical Center (VUmc) with histologically proven distal or mid-rectal carcinomas (MRI 0-10 cm from dentate line) without evidence of distant metastases and eligible for elective laparoscopic TME were included and underwent TaTME. The Ethics Committee of the VUmc approved the protocol. Patients with T4 tumors or those with expected positive circumferential margins prior to neoadjuvant therapy were excluded. A margin of <2 mm was considered positive.

Perioperative assessment

The preoperative assessment included MRI for local staging and computed tomography (CT) of the thorax and abdomen to detect distant metastases. All patients were treated according to the Dutch guidelines for the treatment of rectal cancer. Patients with T2-3 N0-1 tumors underwent preoperative radiotherapy with a total dose of 25 Gy and a daily dose of 5 Gy. Surgery was performed in the week following cessation of radiotherapy. Patients with T2-3 N2 tumors underwent chemoradiotherapy with a total dose of 50 Gy and a daily dose of 2 Gy combined with 5-fluorouracil. In these cases, surgery was performed 6 weeks after the end of the neoadjuvant treatment. From 2014, we changed our national policy and patients with T1, T2 and small T3 have not been given neoadjuvant short-course radiotherapy. Patients received mechanical bowel preparation before surgery with Moviprep (Norgine, Amsterdam, The Netherlands). For postoperative pain control, they received epidural analgesia. Prophylactic antibiotics were administered according to the protocol. Patients were treated according to enhanced recovery after surgery (ERAS) guidelines.

TaTME

The technique we used during the various procedures changed and evolved to a standardized technique. The transanal phase and the abdominal phase were performed in sequence and not synchronous with two teams. In the first patients, we started with the transanal phase of the procedure as described previously. The sequence was changed to a 'transabdominal phase first technique' because of complicating pneumatosis of the retroperitoneum, beginning with standard laparoscopic mobilization of the sigmoid and the splenic flexure. The technique that was used for the laparoscopic mobilization is either a four-trocar medial-to-lateral approach or a single-port approach, with the single-incision laparoscopic surgery (SILS) port at the future ileostomy site, described previously by Van den Boezem et al.[8] During the transabdominal phase, the proximal rectum was mobilized to localize the hypogastric nerves by opening the peritoneal reflection on both sides. We consider it important to leave the anterior part of the peritoneal reflection unopened because it helps to maintain a stable pneumoretroperitoneum during the transanal phase.

The technique used for the transanal phase depended on the height of the tumor. For distal tumors, an intersphincteric dissection was performed with the use of a Scott retractor. This dissection was continued as high up as possible in an open fashion. The rectal stump was then closed with a purse string suture to prevent spillage of tumor cells and bacteria. After closure of the rectal stump, the cavity was rinsed with a povidone-iodine solution as a cytocidal agent. Then, the transanal port was introduced.

In case of more proximal tumors, the rectal stump was closed with a purse string suture either endoscopically or in an open fashion. To secure a total removal of the mesorectum, the purse string is situated 3-4 cm from the dentate line. A full-thickness endoscopic transection of the mucosa was performed using the diathermic hook (Fig. 1A-C). The full-thickness transection circumferentially is essential for optimal use of the pneumorectum and entering the right layer. If not, there is the risk of getting lost in the submucosal plane with the possibility of perforating the rectum.

In the first patients, a SILS Port (Covidien) was used for the rectal dissection. Currently, we use two different ports. For more distal tumors, the SILS port is still used. This port can be sutured to the perineal skin allowing traction to the port to create more space. Furthermore, in case of intersphincteric dissection, suturing the trocars allows to create a pneumorectum, which is otherwise lost due to leakage.

In more proximal tumors, the GelPOINT Path Transanal Access Platform (Applied Medical, Rancho Santa Margarita, California, USA) is used, ergonomically a more pleasant trocar. However, the trocar can be too bulky for distal tumors. The GelPOINT Path has three 10-mm trocars and therefore gives more freedom in the decision which instruments to use. Furthermore, the GelPOINT Path consists of two parts, which are detachable. This allows easy access to the anal canal, making suturing and specimen retraction more accessible.

The pneumorectum was created with carbon dioxide at a pressure of 10-14 mmHg. Initially, the transanal phase was complicated by rhythmic contractions of the rectal wall caused by high flow. After reducing the flow of the carbon dioxide to less than 1 L/min, the contractions ceased.

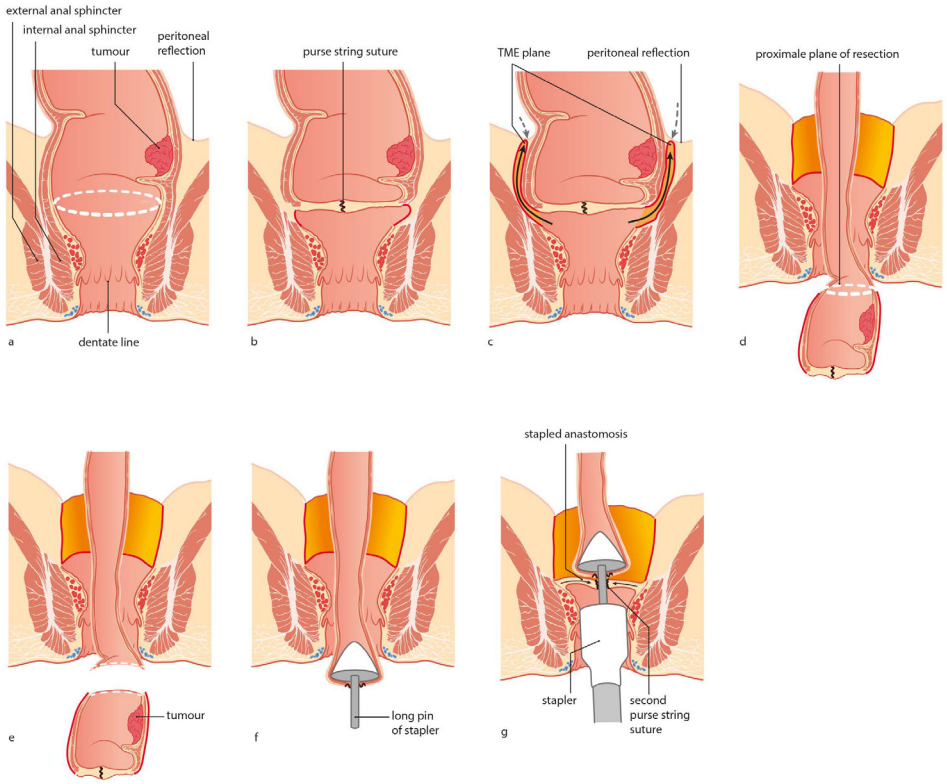
The avascular dorsal plane was developed by sharp dissection with the diathermic hook. It is important to remember that the anal canal is at a steep angle with the pelvis floor and thereby with the TME plane. After dorsal dissection was continued as high up as possible, the dissection was continued ventrally. We used part blunt and part sharp dissection to find the correct plane.

One of the pitfalls of TaTME is dissecting lateral of the TME plane. This will occur when the pelvic floor or parietal fascia is followed from below during dissection, resulting in bleeding or damaging the nerves. Therefore, the dissection of the lateral sides was performed when both the ventral and dorsal dissection was progressing and only the lateral pillar was left. After full TME mobilization, the peritoneum was opened and the specimen was pushed inside, showing the last remaining adhesions.

After the rectosigmoid was completely freed, the specimen is exteriorized transanally under direct visualization by using the camera in the abdominal port (Fig. 1D-E). If the specimen was too bulky, a small abdominal incision was used to extract the specimen.

In case of reconstructing continuity, the sigmoid was divided and the stapler head of the EEA Hemorrhoid stapler (Covidien, Mansfield, Massachusetts, USA) was introduced and the bowel was replaced into the abdomen. The long pin of the stapler is essential for manipulating the proximal bowel. The distal rectal stump was closed with a second purse string suture, and a stapled anastomosis was made after which an ileostomy was created routinely (Fig. 1F-G). In case of no reconstruction, the sigmoid was transected endoscopically. The specimen was removed transanally, and the colostomy was performed.

Figure 1. Steps of TaTME.



A Distal resection margin, B closure with a purse string suture and transection of the mucosa, C mobilization according to TME criteria, D, E transanal specimen removal, F suturing of stapler head, G second purse string and stapled anastomosis.

The figure is published previously in NTVG (Nieuwenhuis DH, Velthuis S, Bonjer J, Sietses C. (2014) [Transanal total mesorectal excision: a new treatment option for rectal cancer]. [Article in Dutch] Ned Tijdschr Geneeskd. 2014; 158: A705) and reprinted with permission.

Results

Eighty consecutive patients were included in this study. Patient characteristics are depicted in Table 1.

Table 1. Patient characteristics

	Overall population (n=80)
Gender	
Male	48
Female	32
Age (years), mean (range)	66.5 (42-86)
BMI (kg/m²), mean (range)	27.5 (19.5-40)
ASA Classification	
ASA I	15
ASA II	53
ASA III	12
Type of resection	
LAR	65
APR	15
Neoadjuvant therapy	
None	15
Radiotherapy	39
Chemoradiotherapy	26

All patients were staged as T2 or T3 carcinomas on preoperative MRI. Depending on preoperative T and N stage, 39 patients were treated with a short course of radiotherapy (5 × 5 Gray), 26 patients were treated with chemoradiotherapy, and 15 patients received no adjuvant therapy. The average distance from the tumor to the dentate linea was 5.3 cm (range 1-10).

Tumor characteristics are depicted in Table 2. Macroscopic examination was graded as complete or nearly complete in 88% of the specimen. Seven of the specimen had minor lacerations, and only two were scored as incomplete (according to the Quirke classification).[9] Positive circumferential resection margins (<2 mm) were seen in two patients. Distal margins were all clear. The average length of the specimen was 19 cm (range 12-28). Average number of lymph nodes was 14 (range 6-30).

Table 2. Tumor characteristics

	Overall population (n=80)
Tumor status (T)	
0	6
1	3
2	29
3	42
N status (N)	
0	44
1	21
2	15
Number of lymph nodes, mean (range)	14 (6-30)
Differentiation of carcinoma	
Well differentiated	27
Moderately differentiated	45
Poorly differentiated	8
Tumor size (cm), mean (range)	3.4 (1.2-11)
Length of resected specimen (cm), median (range)	19 (12-28)
Macroscopic completeness specimen (Quirke)	
Complete	71 (88%)
Nearly complete	7 (9%)
Incomplete	2 (3%)
Circumferential resection margin involvement	
Positive (<2 mm)	2 (2.5%)
Distal resection margin involvement	
Positive (<1cm)	0 (0%)

Laparotomy was recommended and performed in four patients: due to anterior fixation owing to previous radiotherapy for prostate carcinoma in the first patient, due to fixation to the bladder and the left ureter in the second patient, due to possible T4 carcinoma in the third patient and due to cardiac complications that warranted a quick finish of the procedure in the fourth patient.

Intraoperative complications were seen in five patients. Two bleedings occurred due to following the false plane on the lateral side. In three cases, a small perforation had to be sutured on the ventral side. In these three cases, the tumor was located on the dorsal side so none of these perforations resulted in a positive CRM. In seven patients, transanal extraction was not

feasible due to the volume of the specimen and a small abdominal incision was necessary.

Postoperative complications were seen in 39% of the patients. Of these complications, 10 (12%) were graded as severe, Clavien-Dindo grade 3, 4 and 5 (Table 3).

Table 3. Complications according to Clavien-Dindo

	Overall population (n=80)
None	49
Grade 1	8
Grade 2	13
Grade 3	
3a	1
3b	5
Grade 4	
4a	3
4b	0
Grade 5	1

Nine patients were re-operated: one patient because of anastomotic leakage and this patient died postoperatively due to septic complications. Reasons for re-operations in case of grade 4 complications were ischemia of the proximal limb of the colon, anastomotic leakage and small bowel laceration. Four patients with grade 3 complications were re-operated. Reasons were revision of a colostomy because of superficial necrosis, small bowel obstructions due to early adhesions, internal herniation and evacuation of a large hematoma.

One patient was readmitted 10 days after surgery with circular full-thickness ischemia of the mucosa distal of the anastomosis and in the anal canal, possibly caused by pressure necrosis due to the transanally placed trocar. The operative time of this procedure was 183 min.

Median operative time was 204 min, and these times varied considerably (range 91-447). No significant reduction in time was noticed with increased experience. Median hospital stay was 8 days (range 3-41).

Currently, two local recurrences have occurred. The patients were operated 18 and 24 months ago after chemoradiotherapy. Pathology reports showed T3N2 carcinoma in both patients, the specimen showed clear surgical margins in both patients distally, and one of these patients had a positive circumferential resection margin (being <2 mm).

Discussion

The laparoscopic approach for colorectal carcinoma is slowly becoming the standard. Short-term benefits are clear, but oncological superiority over open surgery has not been proven. [7,10-15]

With the use of neoadjuvant therapy, local recurrence rates in rectal cancer have reduced both in open and in laparoscopic surgery. However, most recent results leave room for improvement. The CLASICC trial showed high rates of local recurrence both in the open and in the laparoscopic group.[13]

A recent report of the COLOR II trial shows a high percentage of patients with positive circumferential resection margins.[12]

A further improvement probably warrants the introduction of a new approach. TaTME has been introduced as a supplement to existing laparoscopic techniques to improve results in complex patients. Expectations are high, but we should remember that only small case series have been published. Little is known about long-term functional and oncological results.

The critical words of Wexner and Berho[16] are justified. He correctly stated that we should be cautious not to lose the ground gained in recent decades with the introduction of a new approach.

TaTME was first described in 2011, after which various groups demonstrated feasibility in selected groups of patients. Our group started using the technique in 2012 in unselected patients with distal rectal carcinoma. Showing feasibility, the technique evolved to the standard, currently used in all patients with mid- and distal rectal cancer.

After 80 procedures, our short-term results are comparable with those described in the literature for the standard laparoscopic approach.[12,15] Morbidity and mortality rates conform the type of surgery and might decrease with increased experience. Hospital stay is comparable with standard laparoscopic TME for rectal cancer.[12,15] These data are comparable with those reported in the literature. Fernandez-Hevia et al.[17] recently reported comparable short-term results between standard laparoscopic TME and TaTME from the Barcelona group. This experience did, however, report a reduction in surgical time and a reduced readmission rate.

However, these factors are of relative importance compared with the oncological results. Currently, two local recurrences have developed. It should be noted that follow-up is limited to 2 years. In these early days of TaTME, it is important to critically evaluate the completeness of the mesorectum, since it reflects the oncological quality of the procedure and may influence prognosis. Bosch and Nagtegaal[5] showed an increased risk of local and overall recurrence in patients with incomplete specimens. The specimens reported in this study were graded as complete or nearly complete in 97% of the patients. A positive circumferential resection margin was only seen in two patients. However, patients staged as T4 tumors before neoadjuvant therapy were excluded.

Comparing quality of the specimens after traditional laparoscopic and TaTME, we previously demonstrated that TaTME seems to be associated with significantly higher rate of completeness of the mesorectum.[18]

Various groups currently publish their first data in highly selected cases. Lacy et al.[19] published their first 20 cases, but their experience is currently more than 100. Emhoff et al.[20] recently reviewed all published experience. Overall intraoperative and postoperative complications rates of 8.3 and 27.8%, respectively, are similar to laparoscopic TME. The reported mesorectal fascia was intact in all patients, and 94% had negative margins. Other groups report no oncological recurrence in average-risk patients.

Rouanet et al.[21] are currently the only group who have reported the results in high-risk tumors. Thirty patients with advanced or recurrent low rectal cancer associated with unfavorable anatomical tumor characteristics underwent a sphincter sparing TaTME. They reported four patients with positive margins (87%) compared with 95% negative margins in low-risk patients who underwent laparoscopic TME during the same period. After 21 months, only 13 patients were free of disease. The short-term surgical results are nonetheless acceptable. The authors report no postoperative mortality and 30% morbidity.

These results stress the importance of careful patient selection. The TaTME should first be introduced in low-risk patients with specialized teams. A long-term outcome has to be available before it can be accepted as a valid alternative to standard laparoscopic techniques. Furthermore, non-inferiority or superiority should be proven in randomized trails. Currently, the COLOR III trial, standard laparoscopic TME versus TaTME, is in preparation.

Before randomized trials can start, sufficient amounts of surgeons should be trained. We recently started workshops and proctoring programs for Dutch surgeons. Cadaver training is combined with proctoring in local hospitals.

Conclusion

TaTME is a safe alternative to standard laparoscopic TME in selected low-risk patients with rectal carcinoma when treated by an experienced colorectal team. In the future, randomized trials are necessary to prove oncological safety.

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CHAPTER 8

Clinical outcomes and case volume effect of transanal total mesorectal excision for rectal cancer: a systematic review

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Abstract

Background Transanal Total Mesorectal Excision (TaTME) has been developed to improve quality of TME for patients with mid and low rectal cancer. However, despite enthusiastic uptake and teaching facilities concern exists for safe introduction. TaTME is a complex procedure and potentially a learning curve will hamper clinical outcome. With this systematic review we aim to provide data regarding morbidity and safety of TaTME.

Methods A systematic literature search was performed in MEDLINE (PubMed), Embase (Ovid) and Cochrane Library. Case reports, cohort series and comparative series on TaTME for rectal cancer were included. To evaluate a potential effect of case volume, low volume centres (n≤30 total volume) were compared with high volume centres (n>30 total volume).

Results 33 studies were identified (three case reports, 25 case series, five comparative studies), including 794 patients. Conversion was performed in 3.0% of the procedures. The complication rate was 40.3%, 11.5% were major complications. The quality of the mesorectum was "complete" in 87.6% and the circumferential resection margin (CRM) was involved in 4.7%. In low vs. high volume centres the conversion rate was 4.3% vs. 2.7%, major complication rates were 12.2% vs. 10.5% respectively. TME quality was "complete" in 80.5% vs. 89.7% and CRM involvement was 4.8% and 4.5% in low vs. high volume centres respectively.

Conclusion TaTME for mid and low rectal cancer is a promising technique, however it is associated with considerable morbidity. Safe implementation of the TaTME should include proctoring and quality assurance preferably within a trial setting.

Introduction

Transanal total mesorectal excision (TaTME) has had tremendous attention since its introduction in 2010 by the group of Lacy.[1] The TaTME technique has been developed to improve the quality of the TME procedure for patients with mid and low rectal cancer. In TaTME, the low pelvic mesorectum is approached through the anus using a laparoscopic single port platform. Potentially, TaTME facilitates the quality of dissection and decreases the need for definitive colostomies and conversions to open technique. Moreover, the TaTME technique aims to achieve higher rates of complete specimens, better visual determination of the distal margin and lower rates of involved circumferential resection margin (CRM) compared to abdominal TME. Especially in low rectal cancer surgery relative higher rates of incomplete specimens and higher rates of CRM involvement have been reported compared to tumours located in the upper rectum.[2-11] Mid and low rectal cancer are associated with worse outcome when compared to high rectal cancer due to the difficult access of the lower pelvis. The innovative TaTME technique has the potential to improve these results. However, randomised clinical trials evaluating this new technique are lacking.[12-14]

Despite the potential benefits concern exists for uncontrolled widespread adaptation. TaTME is a complex procedure and a learning curve might influence initial clinical results. Since poor surgical quality in rectal cancer is associated with poor outcome, quality assurance of the new surgical technique seems plausible. Early adaptors of the technique have shown favourable results but new serious complications have also been published.[15-18] Urethra injury or pelvic side wall injury with bleeding and nerve damage have not been documented for the conventional low anterior resection (LAR).[2-11] In addition, increased bacterial load as is observed after TaTME might induce the occurrence of presacral abscesses.[19] Most importantly, data regarding oncological outcome after TaTME for mid and low rectal cancer are still scarce.[12-18] Although the aim is to perform resection with intact specimen, rectal wall perforations are observed which can potentially result in tumour spill.[1,15] Concern exists if luminal contamination with tumour cells of the pelvis results in more recurrences despite a negative resection margin and good quality specimen. In addition to oncological outcome, the long-term functional outcome of the procedure has to be awaited. Potentially, lower anastomosis results in worse functional outcome compared to abdominal laparoscopic TME.

With this systematic review we aim to provide a comprehensive overview of the current data regarding safety of the TaTME procedure reporting on perioperative and oncological results with specific focus on adverse events and outcomes.

Materials and methods

Search strategy

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[20] MEDLINE (PubMed), Embase (Ovid) and the Cochrane Library were searched systematically. The search period was from January 1st 2005 until July 1st 2016. The following search terms were used: (((excision*[tiab] OR resection*[tiab] OR TME[tiab] OR TaTME[tiab] OR TAMIS[tiab] OR NOTES[tiab] OR proctectom*[tiab]) AND (transanal*[tiab] OR trans-anal*[tiab])) OR ((excision*[ot] OR resection*[ot] OR TME[ot] OR TaTME[ot] OR TAMIS[ot] OR NOTES[ot] OR proctectom*[ot]) AND (transanal*[ot] OR trans-anal*[ot]))) AND ((((“Neoplasms”[Mesh] OR neoplas*[tw] OR tumor*[tw] OR tumour*[tw] OR cancer*[tw] OR malignan*[tw] OR oncolog*[tw] OR carcinom*[tw] OR adenocarcinom*[tw]) AND (“Rectum”[Mesh] OR rectum[tiab] OR rectal[tiab] OR colorect*[tiab] OR mesorect*[tiab])) AND (“surgery”[Subheading] OR surgery[tiab] OR surgical[tiab] OR operati*[tiab])) OR (“Rectal Neoplasms/surgery”[Mesh:noexp])). References of the retrieved papers were screened to search for additional reports.

Inclusion and exclusion criteria

Published clinical studies on TaTME for rectal cancer reporting clinical and pathological outcomes were included. Case reports, cohort series and comparative series were eligible. Abstracts, reports with no peer-reviewed data and reports on robotic TaTME were excluded. No restriction was made based on included number of patients. Only articles in European languages were included. Two reviewers independently assessed all titles, abstracts and full texts for potential inclusion. When required, a third reviewer was consulted. Included articles based on full text were checked for overlapping data with other studies. Studies with potential overlapping patient populations were excluded for the overall analysis and subanalysis regarding volume.

Endpoints and data extraction

The primary endpoints of this study were short-term morbidity and specimen outcome. The following data was collected from included studies: first author, year of publication, number of patients, patient and tumour characteristics (gender, BMI, age, ASA classification, tumour distance, clinical TNM stage, neoadjuvant therapy), surgical details (operative time, type of anastomosis, use of diverting ileostomy, approach with synchronous abdominal and transanal resection, intraoperative complications, conversion rate), pathology outcomes (TME quality, involvement of CRM, involvement of distal resection margin, pathological T and N stage) and

postoperative outcomes (hospital stay, postoperative complications, 30-day mortality rate and local and distant recurrence rates after follow-up of 12 months).

Heterogeneity in data on the height of tumour restricted data evaluation. Therefore, height was adjusted using international accepted definitions for anal verge (baseline 0cm), dentate line (+1.9cm) anorectal junction (+4cm).[21-23] Postoperative complications were reported as classified by Clavien-Dindo.[24] Minor complications were defined as complications needing non-invasive treatment (Clavien-Dindo classification I or II), major complications were defined as complications needing invasive treatment (Clavien-Dindo ≥ III).

Subanalysis low volume centres versus high volume centres

To identify a possible difference in outcome depending on the volume in the TaTME technique, subanalysis of all variables was performed comparing low volume centres (n≤30 total volume) with high volume centres (n>30 total volume) and excluding potential (partial) duplicates of cases in publications by centres that published multiple cohort series.[25]

Statistical analysis

For all participating patients from the different included studies, data for several variables were pooled in a way as if the patients participated in one study. The mean of the variable of interest of each included study was multiplied with the number of participants in that study and subsequently all thus obtained products were added up and divided by the total number of participants in all included studies to obtain a pooled mean. For percentages of dichotomous variables of the different studies a comparable method was applied. Because of variation in the studies regarding reporting an overall mean or median for the specified endpoint, the mean percentages and weighted means are based on either mean or median of the reporting studies. Furthermore, ranges are used to show the minimum and maximum of the reported means or medians in the different studies. For comparing numeric variables of low and high volume centres an independent T-test was used. Review Manager version 5.3.5 (2014) was used to calculate the risk difference of dichotomous outcomes of the comparative studies and to make forest plots. To account for clinical heterogeneity, the random effects model based on DerSimonian and Laird's method was used. A p-value < 0.05 was considered statistically significant.

Quality assessment: MINORS instrument

Quality assessment of the included articles was performed using the MINORS instrument, an index for the assessment of non-randomised studies.[26] A total of eight items are scored for non-comparative studies and 12 for comparative studies. The items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). The global ideal score being 16 for non-comparative studies and 24 for comparative studies.

Results

Included studies

The literature search identified a total of 3489 articles (Embase n=2132, PubMed n=1314 and Cochrane Library n=43). 1581 duplicates were removed and 1743 articles were excluded after screening title and reading abstract (performed by both CD and AT), leaving 165 articles for full-text review. Finally, 33 articles fulfilled all the inclusion criteria and met no exclusion criteria and were included for analyses.[1,15-18,27-54] These 33 articles comprised three case reports, 25 case series and five comparative studies (Figure 1). The mean MINORS index of the non-comparative studies was 13 (range 8-15) and of the comparative studies 20 (range 20-21), indicating fair overall quality of the included articles. To correct for overlapping patient populations nine of these studies were not included in the overall analysis (Table 1).

Patient and tumour characteristics

In total 794 patients were included, ranging from one patient to 140 patients per study. The tumour distance was measured from the anal verge in 24 studies, in six from the anorectal junction and in three from the dentate line. With correction for overlapping studies, in total 661 patients were included (444 males (67%) and 217 females (33%)) The calculated distance from the anal verge ranged from 2.0cm to 8.4cm with a weighted mean of 6.3cm. Other baseline and tumour characteristics are shown in Table 2.

Surgical details

The operative time ranged from 166 to 369 minutes with a weighted mean of 243.9 minutes. In nine of the 33 studies two surgical teams performed the surgery in some or all of the cases, one for the laparoscopic abdominal approach and one for the transanal approach, working simultaneously. For studies reporting on TaTME with two teams the weighted mean for the operative time was 209.8 minutes (range 166 to 369) compared to 264.5 minutes (range 204 to 360) with one operating team. Other surgical details are depicted in Table 3.

Figure 1. Flow chart of selection process

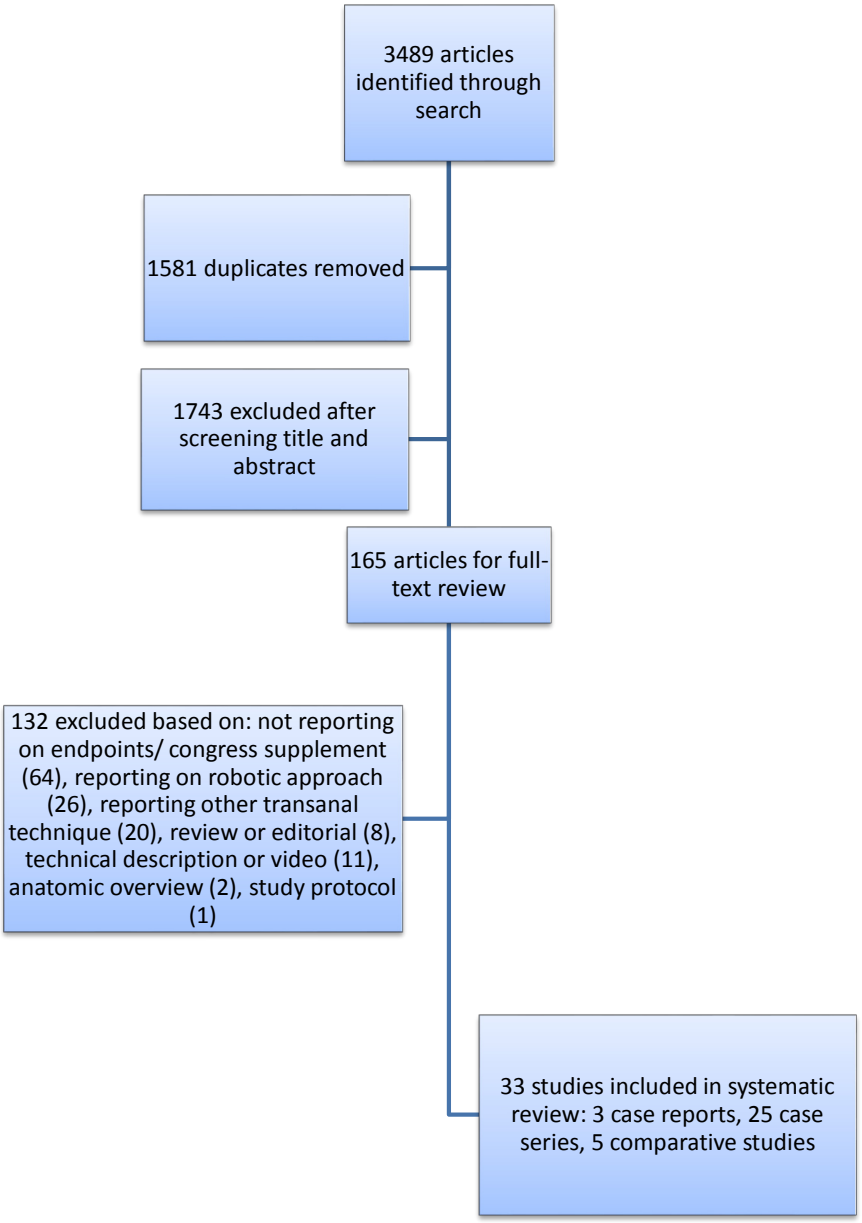


Table 1. Details of included studies

Author	Year publication	N	Gender M	Gender F	BMI (kg/m²)	Age (year)	ASA (mean)	Tumour distance (cm)*
Sylla†	2010	1	0	1	20	76	NR	8
Dumont	2012	4	4	0	23,4	66,8	NR	5,3
Zorron†	2012	2	1	1	NR	65	1	7
Lacy†	2013	3	1	2	21,7	73	NR	9,7
Lacy†	2013	20	11	9	25,3	65	2	6,5
Sylla	2013	5	3	2	25,7	48,6	NR	5,7
Velthuis†	2013	5	2	3	NR	69,4	NR	6
Rouanet	2013	30	30	0	26	65	NR	5
Zhang	2013	1	0	1	20	48	NR	7
Fernandez-Hevia†	2014	37	24	13	23,7	64,5	2	5,8
Velthuis†	2014	25	18	7	25	64	NR	8
Atallah†	2014	20	14	6	24	57	2	5
Chouillard	2014	16	6	10	27,9	57,7	2	8,4
Meng	2014	3	2	1	NR	80	NR	6,2
Zorron	2014	9	5	4	NR	62,6	1	7,56
Veltcamp Helbach	2015	80	48	32	27,5	66,5	NR	7,2
Tuech	2015	56	41	15	27	65	2	4
Muratore	2015	26	16	10	26,2	65,8	NR	4,4
Elmore	2015	6	2	4	25	61,3	2	5,5
Knol	2015	10	8	2	26,5	60,5	NR	6,89
Serra-Aracil	2015	32	24	8	25	68	2	8
Lacy	2015	140	89	51	25,2	65,5	2	7,6
Perdawood	2015	25	19	6	28	70	2	8
McLemore	2015	1	1	0	32	66	NR	2
Buchs†	2015	20	14	6	27,1	59,3	2	6
Chen	2015	50	38	12	24,2	57,3	2	5,8
Prochazka	2015	17	11	6	28	68	3	6,0
Rink	2015	24	18	6	25	57	2	5
Burke	2016	50	30	20	26	56,5	2	4,4
Rasulov	2016	22	11	11	26	56	NR	6,5
Marks	2016	4	1	3	26	56	NR	5,1
Foo	2016	10	5	5	23,4	62,2	2	5,1
Buchs	2016	40	32	8	27,4	64,4	2	7

Table 1. Continued.

Author	Year publication	N	Conversion (%)	TME quality (%) Complete¶	Positive distal resection margin (%)	CRM involvement (%)	pT3+ (%)	Harvested lymph nodes (N)
Sylla†	2010	1	0	100	0	0	0	23
Dumont	2012	4	0	NR	0	0	NR	16
Zorron†	2012	2	0	NR	0	0	100	11,5
Lacy†	2013	3	0	NR	0	0	66,7	NR
Lacy†	2013	20	0	NR	0	0	NR	15,9
Sylla	2013	5	0	100	0	0	0	33
Velthuis†	2013	5	NR	100	0	0	40	12
Rouanet	2013	30	6,7	100	0	0	100	12
Zhang	2013	1	0	100	0	13,3	70	13
Fernandez-Hevia†	2014	37	0	91,9	NR	0	62,2	14,3
Velthuis†	2014	25	NR	96	NR	4	NR	14
Atallah†	2014	20	NR	55	5	5	55	22,5
Chouillard	2014	16	6,3	NR	0	0	50,1	21
Meng	2014	3	0	NR	0	0	66,7	NR
Zorron	2014	9	22	NR	0	11	66,7	13
Veltcamp Helbach	2015	80	5	88,8	0	2,5	52,5	14
Tuech	2015	56	5,4	83,9	0	5,4	39,3	12
Muratore	2015	26	0	88,5	0	0	30,8	8
Elmore	2015	6	0	100	0	0	50	32
Knol	2015	10	0	90	0	0	40	10,5
Serra-Aracil	2015	32	0	93,8	0	0	NR	15
Lacy	2015	140	0	97,1	0	6,4	NR	14,7
Perdawood	2015	25	0	80	NR	4	68	21
McLemore	2015	1	0	100	NR	NR	0	13
Buchs†	2015	20	15	80	0	5,9	25	23,3
Chen	2015	50	2	NR	NR	4	NR	16,7
Prochazka	2015	17	0	47,1	0	11,8	35,3	10
Rink	2015	24	NR	91,67	0	8,3	33,3	14
Burke	2016	50	2,2	72	2	4,0	50	18
Rasulov	2016	22	4	68	NR	5,0	23	17
Marks	2016	4	0	100	0	0,0	25	6
Foo	2016	10	10	60	0	0,0	NR	15,6
Buchs	2016	40	7,5	92,5	0	5,0	32,5	20

Table 1. Continued.

Author	Year publication	N	Hospital stay (days)	Postoperative complications (%) Minor¥	Major¥	30-day mortality (%)
Sylla†	2010	1	4	0	0	0
Dumont	2012	4	13	0	25	0
Zorron†	2012	2	6	50	0	0
Lacy†	2013	3	4,7	33,3	0	0
Lacy†	2013	20	6,5	20	0	0
Sylla	2013	5	5,2	60	0	0
Velthuis†	2013	5	NR	40	20	NR
Rouanet	2013	30	14	33,3	13,3	0
Zhang	2013	1	NR	0	0	0
Fernandez-Hevia†	2014	37	6,8	24,3	8,1	0
Velthuis†	2014	25	NR	NR	NR	NR
Atallah†	2014	20	4,5	75	25	0
Chouillard	2014	16	NR	0	18,8	0
Meng	2014	3	6,5	0	0	NR
Zorron	2014	9	7,6	11,1	11,1	0
Veltcamp Helbach	2015	80	8	26,3	12,5	1
Tuech	2015	56	10	19,6	5,4	0
Muratore	2015	26	7	15,4	11,5	3,8
Elmore	2015	6	10,3	0	33,3	0
Knol	2015	10	6	20	0	0
Serra-Aracil	2015	32	8	18,8	25	0
Lacy	2015	140	6	36,4	10	0
Perdawood	2015	25	5	28	24	0
McLemore	2015	1	7	100	100	0
Buchs†	2015	20	7	25	10	0
Chen	2015	50	7,4	20	6	0
Prochazka	2015	17	9	23,5	11,8	0
Rink	2015	24	NR	12,5	12,5	0
Burke	2016	50	4,5	28	18	0
Rasulov	2016	22	8	27	0	0
Marks	2016	4	5	25	0	0
Foo	2016	10	6	20	0	0
Buchs	2016	40	7,5	27,5	12,5	0

† *Potentially overlapping patient population*
* *Measured from anal verge*
¶ *Defined by Quirke*
¥ *Minor was defined as Clavien-Dindo classification I or II, major was defined as ≥ III*

Table 2. Baseline and tumour characteristics

	Weighted mean	Range
Gender (%)		
M	67	
F	33	
BMI (kg/m2)	26.1	20-32
Age (years)	63.4	48-80
ASA (mean)	2	1-3
Tumour distance (cm)*	6.3	2-8.4
cT3-T4 (%)	71.6	40-100
Neoadjuvant therapy (%)	72.5	28-100

** Measured from anal verge*

Table 3. Surgical details and clinical outcomes

	Weighted mean	Range
Conversion (%)	3.0	0-22
Postoperative complications (%)		
Minor*	28.8	0-100
Major*	11.5	0-100
Operative time (min)	243.9	166-369
Coloanal handsewn anastomosis (%)**	53.9	0-100
Diverting ileostomy (%)***	90.3	25-100
Colostomy (%)***	4.7	0-28
2 team approach (%)	37.5	0-100
Hospital stay (days)	8.4	4.5-14
30-day mortality (%)	0.3	0-3.8

** Minor was defined as Clavien-Dindo classification I or II, major was defined as ≥ III*
*** % of total patients with anastomosis*
**** % of total patients*

Procedure related complications

In 18 studies no intra-operative complications were reported, in one study no major complications and in two studies the number of intra-operative complications was not mentioned. Of the 12 studies that did report intra-operative complications, five patients experienced side wall damage and five patients urethral damage during surgery. In two patients the urethral lesion was repaired with sutures during the procedure not resulting in any documented problems postoperatively. In one patient the lesion was managed nonoperatively and no long-term sequelae were documented. In the other patients with urethral injury the repair and outcome were not described. In four of the patients with side wall damage, the lesions were small without major postoperative morbidity, in the other patient outcome was not reported. One study reported early intraperitoneal CO2 leakage hampering the procedure. In one case extensive pneumatosis of the retroperitoneum and mesentery of the small bowel was observed which stopped the procedure but did not result in any postoperative morbidity. One patient experienced an air embolism with temporary oxygen desaturation. In ten patients bleeding occurred, in five the source was the pelvic side wall, in three the bleeding was located presacrally, in one patient the bleeding was the result of injury to the iliac vessels and in another patient the bleeding it was located at the left side of the mesorectum. Finally, in one patient intraoperative bladder injury occurred. The defect was closed laparoscopically and treated with a urinary catheter for one week.

Pathology outcomes

At histopathological examination, different descriptions were used to define the quality of the mesorectum hampering accurate comparison. In the studies using the definition based on Quirke's classification (n=19), the weighted mean of the quality of the mesorectum was "complete" in 87.6% and "nearly complete" in 10.9%. Positive distal resection margins were found in 0.2% of the patients. The rate of involvement of CRM was 4.7%. In 45.2% of the patients a pT3 or pT4 tumour was found at pathological examination (Table 4).

Table 4. Pathology outcomes and follow-up

	Weighted mean	Range
TME quality (%)*		
Complete	87.6	47.1-100
Nearly complete	10.9	0-52.9
Incomplete	1.5	0-18
Distal resection margin involvement (%)	0.2	0-2
CRM involvement (%)	4.7	0-13.3
pT3-T4 (%)	45.2	0-100
Recurrence**		
Local (%)	4	0-16.7
Distant (%)	8.1	5.4-14
Follow-up (months)	18.9	15.1-29

** Defined by Quirke*
*** Only > 12 months*

Postoperative outcomes and complications

The duration of hospital stay ranged from 4.5 to 14 days with a weighted mean of 8.4 days. Total complication rate was 40.3%. Complications reported were: anastomotic leak (37), urinary retention and urinary dysfunction (26), ileus (32), obstruction and intestinal occlusion (15), presacral abscess and pelvic sepsis (18), increased ileostomy output (16), blood transfusion (11), anastomotic stricture (11), hemorrhage (6), bleeding (6), (organ cavity) surgical site infection (8), fever (6), intra-abdominal collection (5), colitis after ileostomy closure (4), nosocomial infection (3), pneumonia (3), small bowel laceration (2), rectovaginal fistula (2), resection of ischemic conduit (2), peri-anastomotic fluid collections (2), wound infection (2), acute renal failure (1), anastomotic fistula (1), ureteral stent placement (1), ischemia of the proximal limb of the colon (1), anastomotic sinus (1), superficial necrosis of colostomy (1), early adhesions (1), internal herniation (1), large hematoma (1), cerebral infarction (1), peritonitis (1), pelvic haematoma (2), septic shock (1), inguinal lymphorrea (1), myocardial infarction (1), pulmonary embolism (1), pelvic collection (1), bilateral calf compartment syndrome (1), prolapsing ischaemic anal mucosa (1), perineal wound dehiscence after proctocolectomy (1), gastroparesis (1), necrosis of descending colon due to injury to marginal artery (1), transient paresthesia of both feet due to intraoperative positioning (1), ascites (1), acute postoperative pancreatitis (1), pseudomembranous colitis (1), necrosis of stoma (1), enterostomy-related other (1). Postoperative complications defined as minor occurred in 29.5% (range 0% to 100%) and major complications occurred in 11.3% (range 0% to 100%). 30-day postoperative mortality occurred in two patients in two dif-

ferent studies, accounting for a weighted mean of 0.3%. One patient suffered from anastomotic leak and died after re-operation due to septic complications. The other patient died three days after the operation as a result of myocardial infarction (Table 3).

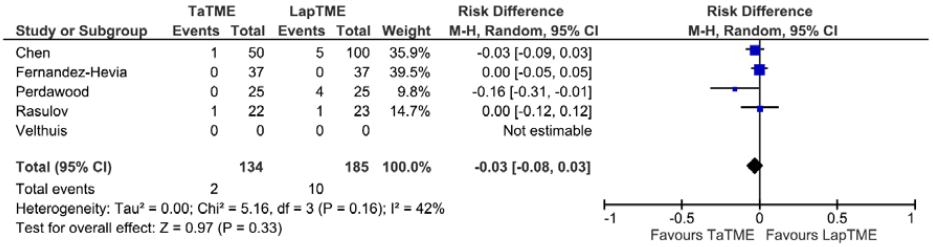
Long-term oncological outcomes

None of the studies had three year complete follow-up to calculate 3-year disease-free survival. Five studies (including 302 patients) reported follow-up of more than 12 months. Overall time of follow-up was 18.9 months. The local and distant recurrence rates were 4.0% and 8.1% respectively (Table 4). In one of these studies five local recurrences occurred during the follow-up period of 21 months. Another study reported two local recurrences, as well as three lung metastases at median follow-up of 29 months. Further, ovarian metastases (one) and para-aortic lymph node metastases (one) were reported in another study after a mean follow-up of 23 months. Another study reported one patient with local recurrence, eight patients with systemic recurrences and two patients with local and systemic recurrence at a median follow-up of 15.1 months. Finally, one study reported two patients with local recurrences and seven patients who developed distant metastases at a median follow-up of 15.1 months.

Comparative studies

Five of the included studies evaluated laparoscopic TME versus TaTME in a case matched study design. Subanalysis of these five studies showed that the weighted means of conversion were 5.4% vs. 1.4% for laparoscopic TME and TaTME, respectively. The risk difference of conversion was -0.03 (95% CI -0.08-0.03; p=0.33). For postoperative complications the weighted means were 34.0% vs. 30.4%, respectively, with a risk difference of -0.10 (95% CI -0.27-0.06; p=0.22). TME completeness was reported in 75.2% in the laparoscopic TME group and 82.8% in the TaTME group. The risk difference was -0.01 (95% CI -0.07-0.05; p=0.72). The weighted means of involvement of CRM were 7.6% in the laparoscopic TME group and 3.2% in the TaTME group with a risk difference of 0.07 (95% CI -0.08-0.21; p=0.37) (Figure 2).

Figure 2. Comparative studies



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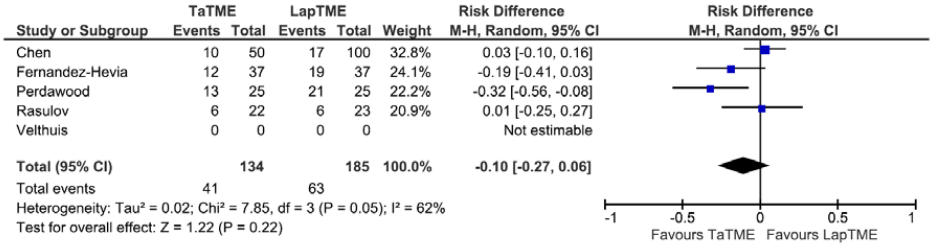
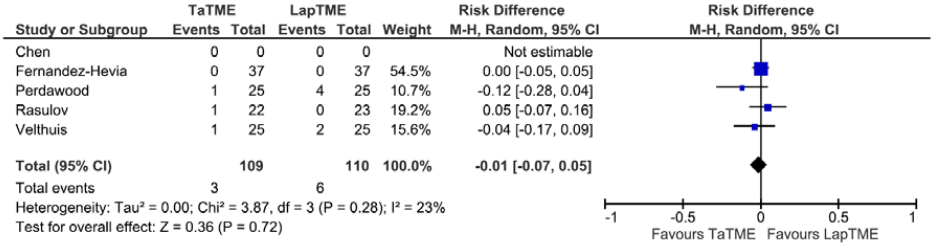
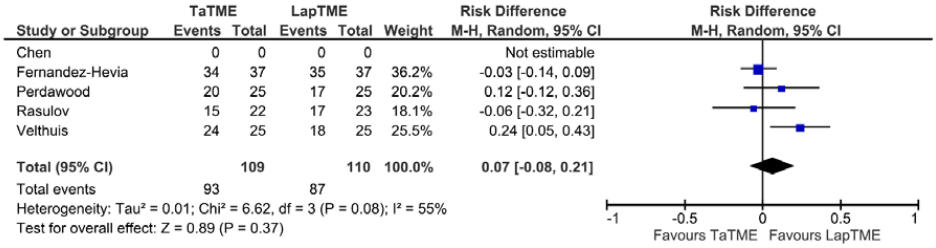


Postoperative complications



CRM



TME completeness

Outcome in low versus high volume centres

The centres with a volume of ≤30 patients were compared to the centres with a volume of >30 patients. Regarding surgical details, operative time was shorter in the high volume centres (222.2 minutes vs. 282.5 minutes) and the procedure was more often performed with a two team approach compared to low volume centres (51.3% vs. 13.7%). Furthermore, the conversion rate was 4.3% in low volume centres and 2.7% in high volume centres. The TME quality was more often assessed as "complete" in high volume centres (80.5% vs. 89.7%) and CRM involvement was 4.8% and 4.5% respectively. Overall complications were comparable but the major complication rate was lower in high volume centres (12.2% vs. 10.5%) (Figure 3). Long-term oncological data revealed a local recurrence rate of 8.9% vs. 2.8% and distant recurrence rate of 7.7% vs. 8.1% for the low and high volume centres respectively, although the number of patients with long-term follow-up was limited (Table 5).

Figure 3. Comparison low versus high volume centres

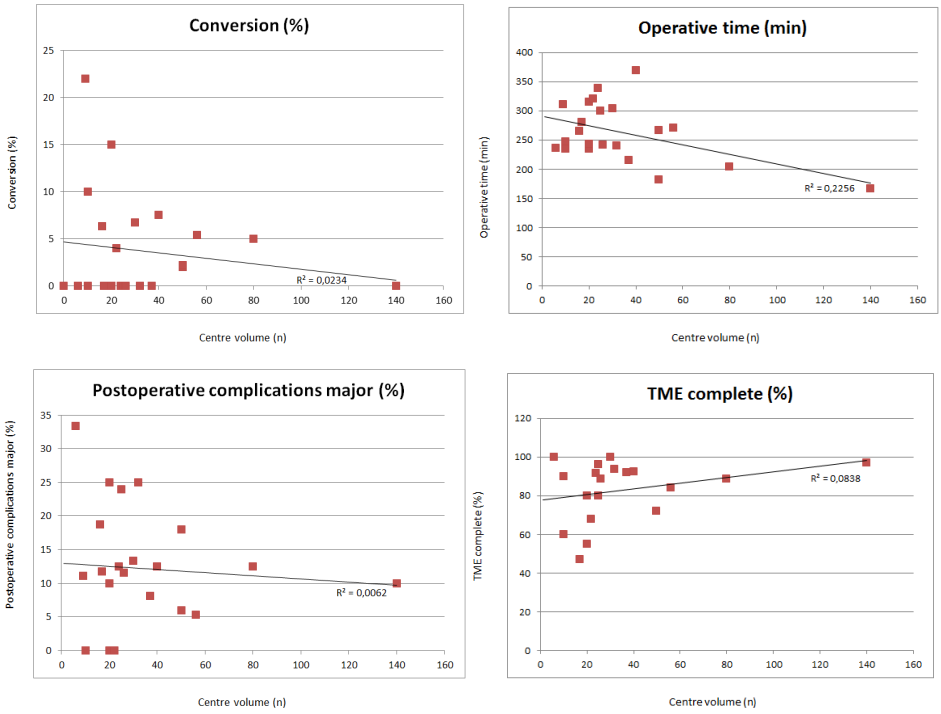


Table 5. Comparison low and high volume centres

	Low volume centres (n≤30) Weighted mean	High volume centres (n>30) Weighted mean
Conversion (%)	4.3	2.7
Postoperative complications (%) Minor¥	21.9	25.2
Postoperative complications (%) Major¥	12.2	10.5
TME quality (%) Complete¶	80.5	89.7
TME quality (%) Nearly complete¶	15.1	9.0
TME quality (%) Incomplete¶	4.0	1.3
Distal resection margin involvement (%)	0.4	0.3
CRM involvement (%)	4.8	4.5
pT3-T4 (%)	44.3	45.1
Gender M (%)	65.8	67.4
Gender F (%)	34.2	32.6
BMI (kg/m^2)	26.1	26.0
Age (years)	62.3	63.8
ASA (mean)	2	2
Tumour distance (cm)*	6.0	6.5
cT3-T4 (%)	71.3	69.3
Neoadjuvant therapy (%)	69.8	73.0
Operative time (min)	282.5	222.2
Coloanal handsewn anastomosis (%)**	62.6	46.8
Diverting ileostomy (%)***	89.8	88.8
Colostomy (%)***	6.8	4.8
2 team approach (%)	13.7	51.3
Hospital stay (days)	6.6	6.5
30-day mortality (%)	0.4	0.2
Recurrence Local (%)†	8.9	2.8
Recurrence Distant (%)†	7.7	8.1
Follow-up (months)†	21.9	18.3

** Measured from anal verge*
*** % of total patients with anastomosis*
**** % of total patients*
¥ Minor was defined as Clavien-Dindo classification I or II, major was defined as ≥ III
¶ Defined by Quirke
† Only > 12 months

Discussion

This systematic review shows that the TaTME procedure is feasible and safe. The technique is associated with substantial morbidity with comparable rates as reported for laparoscopic abdominal TME. The outcome in terms of specimen quality and CRM rate seems adequate with 87.6% and 4.7% respectively. In addition, concern exists for the long-term local recurrence rate which is relatively high (4%) despite a relative short follow-up period (18.9 months). Although numbers are insufficient to draw real conclusions yet and no significance was reached, subanalysis from case match control studies shows that TME has substantial lower conversion rate compared with the laparoscopic TME group. The weighted mean of the conversion rate in laparoscopic TME was 5.4% versus 1.4% in the TaTME group. Furthermore, specimen completeness was higher in the TaTME group (82.8%) than in the laparoscopic TME group (75.2%) and less patients had involvement of CRM in the TaTME group compared with the laparoscopic group (3.2% versus 7.6%).

The outcome parameters seem dependent on the volume since small volume centres report longer operation time and higher conversion rate. Furthermore, worse postoperative outcomes (higher colostomy rate, major morbidity, local recurrence rate and lower rate of complete specimens) are observed as compared to the high volume cohorts.

The total morbidity of the TaTME procedure in this systematic review is comparable with the conventional laparoscopic TME as published in the large randomised trials which display 37-54% total complications.[2-11] Fernandez-Hévia et al. showed a decrease in morbidity including decreased rate of anastomotic leakage compared to conventional TME surgery.[35] This systematic review does not clearly show advantage of the TaTME over the published morbidity rate of LAR. One of the most frequent complications reported was anastomotic leakage which occurred in 37 out of 646 patients with anastomosis (5.7%). The leakage rate compares favourably to reported leakage rates from laparoscopic TME at approximately 10% and this might be an advantage of the TaTME, although randomised data has to be awaited.[5] New possible hazardous complications for TaTME are reported, as urethral lesions and damage of the pelvic side wall which are a concern and need further attention in education. Furthermore, urinary disorders were reported in 26 patients (3.3%) and pelvic abscesses/sepsis in 18 out of 794 patients (2.3%). The reported incidence of presacral abscesses was not increased compared to the abdominal TME procedure. This is unexpected since it has been shown that increased bacterial load is present in the pelvis after TaTME.[19] The low rate of conversions compared to reported laparoscopic TME seems a major improvement and might

be accounted as a benefit of TaTME. The reported colostomy rate is very low but no conclusions can be drawn since considerable selection bias is present since cohort studies do not present intention-to-treat results.

Another potential advantage of the TaTME is improvement in oncological outcome. Surgical specimen quality defined by 1. mesorectal completeness, 2. CRM and 3. distal margins has been shown to be the most important prognostic factor predicting local recurrences.[55] Due to better visualisation in the deep pelvis, meticulous resection can be performed. Cohort and case series of TaTME for rectal cancer included in this systematic review have shown that 2.2% of the specimens was judged as incomplete. In 87% of the cases the resected specimens were considered intact. In two of the largest randomised trials concerning laparoscopic rectal cancer surgery the reported rates of complete specimens were 72% and 88%.[2,5] Another potential improvement in oncological outcome after TaTME is decrease in involvement of CRM. The average involved CRM rate after laparoscopic abdominal rectal resection in large randomised trials including TME is 6-8%.[2-10] This systematic review shows an involved CRM rate of 4.3% after TaTME. CRM is a most significant prognostic factor for local recurrences and might relate to the expertise of the surgeon. Positive distal resection margins were found in 0.3% of the patients. These objective surgical quality measurements compare favourably to the published surgical laparoscopic rectal cancer studies, especially since the majority of the data is obtained from mid and low rectal cancer, whereas the large laparoscopic trials include low, mid and high rectal cancers.[2-10] It is debatable is if these data from cohort series can be compared to an audited clinical (randomised) trial. Nevertheless, TaTME potentially shows benefits over the laparoscopic TME regarding these oncological outcomes.

In the major trials investigating laparoscopic surgery for rectal cancer the local recurrence rate for mid and low rectal cancer is approximately 5% after three years.[6-8,11] The local recurrence rate as shown in this systematic review is 4%. However, this number is likely an underestimation due to the inadequate length of follow-up (18.9 months) and inadequate number of studies reporting follow-up. Interestingly, the involved CRM rate was similar to the local recurrence rate. Concern regarding intraluminal spread or other unknown factors exist but it has to be noted that due to inadequate numbers and lack of long-term oncological follow-up preferably from randomised data no conclusions can be drawn.

This systematic review evidently shows a relationship between case volume and outcomes. Higher volume centres have better outcome compared to small volume centres. Although statistical significance could not be obtained since lack of orginal data including standard

deviations, a clear trend is visible. Operative time and conversion rate were lower and the use of two simultaneous teams for the abdominal phase and the transanal phase during TaTME was performed more frequently in the high volume centres compared to small volume centres. More interestingly, both quality of the resection and postoperative outcome were better in high volume centres. However, an actual learning curve could not be extracted from the included studies, as a proficiency curve has yet to be determined and individual rates of series and outcomes were unavailable.

These data reflect the relative difficulty of the procedure requiring multiple skills including Single Incision Laparoscopic Surgery (SILS) technique and two team operating. As is known from colon surgery and esophageal surgery higher volume is associated with better outcomes. [25] For TaTME this equation seems equal to the other difficult procedures. Although the quality of the data is non-randomised this difference seems valid and calls for education, training and proctoring in order to have a safe introduction of the TaTME technique. A well designed trial in which surgical quality assurance is an essential component should be ideal to evaluate the potential benefit of the TaTME technique. Before entering the trial a surgeon should be trained and proctored and its surgical performance should be objectively monitored in order to exclude underperformance within the trial.

A major limitation of the available data is the lack of randomised evidence. Current cohort data are the result of the pioneers. The TaTME technique is technically demanding of both surgeon and team and requires a learning curve. Another limitation of this and previous systematic reviews is that the included studies are heterogeneous concerning clinical and tumour characteristics, surgical details and reporting of complications. Therefore, comparison of these studies and outcomes of this review should be carefully interpreted. Moreover, most of the studies include same patients in different reports. Abstracts, congress supplements and other unpublished data were not included with the aim to exclude major bias in contrast to previous published reviews. Furthermore, in the low versus high volume analysis, all (partial) duplicate publications were excluded. Nonetheless, most papers represent a small number of patients and high quality studies are lacking. In the absence of published data concerning a learning curve or number of cases to achieve proficiency, we choose to use a cut-off point of 30 based on the traditional rectal surgery and agreement of the consensus group. We realise that this subanalysis is prone to bias. Furthermore, the majority of the studies exclude tumours with ingrowth in surrounding tissues. Especially rectal cancer surgery in patients with T4 tumours is challenging and needs improvement, in specific regarding the quality of the resected specimen. Finally, adequate follow-up period of most studies is lacking and hampering any firm conclusions about long-term outcome.

Nevertheless, even at this early stage of implementation of the TaTME technique, it is important to provide a critical overview of the experience and outcomes of the procedure worldwide and especially to highlight the technical difficulty and possible hazardous aspects of TaTME. The TaTME consensus group has stated that at least 14 procedures a year have to be performed in order to assure optimal quality of the procedure.[56] To ensure save implementation and consistency in surgical quality, several TaTME expert centres across Europe and the US provide training workshops and facilitate proctoring of the technique. Within the context of a future randomised controlled trial quality assurance of this new technique seems of paramount importance.

In conclusion, TaTME is a potential advantageous procedure for mid and low rectal cancer. Despite the current data available is mainly based on expert centres, considerable morbidity has been reported. In order to avoid unwanted negative outcome associated with widespread uncontrolled use of this novel technique, quality assurance and controlled safe implementation seems essential. TaTME has high potential, however extensive evaluation in a well-designed multicentre randomised trial is needed to come to unequivocal conclusions.

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CHAPTER 9

COLOR III: a multicentre randomised clinical trial comparing transanal TME versus laparoscopic TME for mid and low rectal cancer

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Abstract

Introduction Total mesorectal excision (TME) is an essential component of surgical management of rectal cancer. Both open and laparoscopic TME have been proven to be oncologically safe. However, it remains a challenge to achieve complete TME with clear circumferential resections margin (CRM) with the conventional transabdominal approach, particularly in mid and low rectal tumours. Transanal TME (TaTME) was developed to improve oncological and functional outcomes of patients with mid and low rectal cancer.

Methods An international, multicentre, superiority, randomised trial was designed to compare TaTME and conventional laparoscopic TME as the surgical treatment of mid and low rectal carcinomas. The primary endpoint is involved CRM. Secondary endpoints include completeness of mesorectum, residual mesorectum, morbidity and mortality, local recurrence, disease-free and overall survival, percentage of sphincter-saving procedures, functional outcome and quality of life. A Quality Assurance Protocol including centralised MRI review, histopathology re-evaluation, standardisation of surgical techniques, and monitoring and assessment of surgical quality will be conducted.

Discussion The difference in involvement of CRM between the two treatment strategies is thought to be in favour of the TaTME. TaTME is therefore expected to be superior to laparoscopic TME in terms of oncological outcomes in case of mid and low rectal carcinomas.

Annually approximately 737,000 patients are diagnosed with rectal cancer worldwide.[1] The standard potentially curative treatment of rectal cancer is total mesorectal excision (TME). With the introduction of laparoscopic TME, concerns arose about the oncological safety. The COlorectal cancer Laparoscopic or Open Resection (COLOR) II trial demonstrated improved short-term outcomes and similar long-term outcomes after laparoscopic resection of rectal cancer, compared with open resection.[2,3]

However, particularly resection of mid and low rectal cancer is technically demanding due to tapering of the mesorectum in the pelvis and the forward angle of the distal rectum rendering this part of the rectum less accessible from the abdominal cavity. These factors predispose to incomplete mesorectal excision and involved circumferential resection margins (CRMs), with consequent local recurrences. Moreover, high morbidity rates are reported as result of poor anastomotic techniques and high conversion rates because of the limited view on the distal margin of the tumour and difficult mobilisation in the narrow pelvis. Despite the increasing uptake of laparoscopic TME in the treatment of rectal cancer, conversion rates to open procedures are reported up to 34%.[2,4,5] Conversion is frequently needed in male, obese patients or in case of bulky or distally located tumours. Furthermore, mid and low rectal cancer surgery is associated with poor functional outcome with high colostomy rates compared to high rectal cancer.[2] Large randomised trials reported rates of abdominoperineal resection (APR) in laparoscopic rectal cancer resection of 25-29%.[2,4]

To improve visualisation and potentially improve functional and oncological results, the transabdominal transanal (TATA) technique was introduced in the 1990's, which included an open approach from below to rectal tumours located in the distal one-third of the rectum [6]. The use of single port laparoscopic platforms has enabled the introduction of transanal TME (TaTME) by Lacy in 2010. Both techniques have in common to adhere to TME principles, achieving tumour-free distal and circumferential margins (CRMs) and harvesting a minimum of 12 lymph nodes for pathological assessment.[7] The TaTME technique takes the most important developments in rectal cancer surgery from the last 30 years and combines them into one surgical technique.[8]

TaTME for mid and low rectal cancer has potential benefits: better specimen quality with better radicality, less morbidity as result of better anastomotic techniques and less conversions and more sphincter-saving rectal resections without compromising oncological outcomes.

Several groups have already demonstrated that TaTME can be performed safely with a promising amount of intact specimens and low rates of involved CRM.[9-14] The next crucial step of assessing a surgical innovation is a randomised controlled trial. Therefore, a randomised trial is needed to evaluate the role of TaTME in rectal cancer and to assess oncological outcomes. The COLOR III trial has been designed to compare short- and long-term outcomes of transanal and laparoscopic TME for mid and low rectal cancer.

Patients and methods

COLOR III trial is an international, multicentre, superiority, randomised trial comparing TaTME and laparoscopic TME as the surgical treatment of mid and low rectal carcinomas.

Eligibility

A total of 1098 consecutive patients scheduled for resection of a solitary mid or low rectal carcinoma (5-10 and 0-5 cm from anal verge on MRI) will be included in the COLOR III trial. Patients with stage I-III rectal cancer for whom TME is indicated, suitable for elective resection, with a rectal carcinoma observed at colonoscopy and histologically proven through biopsy are eligible. The distal border of the tumour has to be within 10 cm of the anal verge on MRI scan. A CT scan of the thorax and abdomen should be performed to exclude distant metastases. Patients after neoadjuvant therapy, patients with any BMI, as well as patients with previous abdominal or pelvic surgery can be included. Furthermore, patients with tumours that are downstaged can be included. This means patients with a distance of <2 mm between tumour and mesorectal fascia, tumour ingrowth in the anal sphincter complex or m. levator ani or T4 tumours having: distance more than 2 mm between tumour and mesorectal fascia, no ingrowth or no T4 tumour after neoadjuvant therapy can be included. Informed consent will be obtained from all eligible patients in accordance with the requirements of the local ethical board.

Exclusion criteria are T1 tumours which can be treated by local excision, T3 tumours with margins <1 mm to the endopelvic fascia, tumours with ingrowth in the internal sphincter or m. levator ani and all T4 tumours as staged through MRI scan prior to neoadjuvant therapy. Other causes for exclusion are previous rectal surgery, pregnancy, age <18 years, absolute contraindications to general anaesthesia or prolonged pneumoperitoneum (ASA score of more than III), signs of acute intestinal obstruction or synchronous abdominal surgery. Furthermore, a medical history of familial adenomatous polyposis coli, hereditary non-polyposis colorectal cancer, active Crohn's disease or colitis ulcerosa or other malignancies, except adequately treated basocellular skin carcinoma or in situ cervix uteri carcinoma, will result in exclusion.

All participating centres in the COLOR III trial will keep the coordinating centre informed of all patients presenting with rectal cancer. Data on patients with rectal cancer who are not included in the COLOR III trial will be registered.

Randomisation

Once eligibility has been established, patient details have been noted and the preoperative MRI is centrally reviewed, patients will be allocated to either transanal or laparoscopic TME. Randomisation will be performed by computer through the internet and will be stratified for preoperative (chemo)radiotherapy, T-stage, height of the tumour (mid or low) and gender. Patients will be randomised in a 2:1 ratio, in favour of the TaTME. Data will be analysed on 'intention to treat' basis in case patients are not subjected to the randomised treatment modality.

Surgical procedure

Included surgical procedures to obtain TME are: 1. low anterior resection (LAR) with colorectal anastomosis, 2. LAR with coloanal anastomosis and 3. intersphincteric abdominoperineal resection (APR).

Excluded is an extralevator abdominoperineal excision (ELAP) (indicated in patients with tumour ingrowth in the anal sphincter complex or m. levator ani).

Complete laparoscopic excision of the total mesorectum is mandatory to qualify the procedure as a 'laparoscopic TME'. The level of transection of the inferior mesenteric artery is up to the surgeon's preference. Both right and left hypogastric nerves should be preserved. The splenic flexure should be mobilised when undue tension at the anastomosis is likely. Other aspects of the surgical procedure such as type of anastomosis, use of diverting ileostomy and drainage of surgical field are up to the discretion of the surgeon.

In TaTME, the rectum is being mobilised transanally according to TME principles. TaTME is defined as dissection of the distal one-third of the mesorectum. After resection of the rectum and the mesorectum, a hand sewed or stapled anastomosis is created according to the preference of the performing surgeon, as well as creation of a diversion ileostomy and drainage of the surgical field.

In both treatment arms, the use of single port as well as multiport laparoscopy is allowed for the abdominal part of the procedure. Robotic TME is not allowed, since robotic TME possibly results in different primary and secondary endpoint results compared with laparoscopic TME.

In TaTME, conversion (to either laparoscopic or open TME) is defined as interruption of transanal TME due to technical difficulties or complications during transanal dissection, requiring

completion of the majority of the TME using an abdominal approach. In laparoscopic TME, conversion is defined when completion of the dissection of the mesorectum is performed through a traditional open abdominal or transanal approach. Conversion is determined by the surgeon in case of concerns about patient safety, technical difficulties and inability to complete the TME procedure adequately or associated conditions that require treatment.

COLOR III trial quality assurance

To ensure both surgical quality and centre capability to adhere to the study protocol, including the recruitment process and data collection, the COLOR III trial Quality Assurance Protocol has been developed and will be applied before entering into the trial.

To evaluate surgical quality, a Quality Assurance Manual and a Competency Assessment Tool for technical and oncological quality for laparoscopic and TaTME within the scope of COLOR III have been developed. These will be used for surgeon selection into the trial and to measure adherence to agreed surgical quality standards during the trial. A Delphi methodology has been applied with a peer-nominated international group of expert colorectal consultants in the TaTME technique in order to develop a technical manual and operation logbook. A TaTME Competency Assessment Tool was developed based on the results of the Delphi methodology. This tool has been validated in order to ensure acceptable reliability and validity standards prior to its implementation in the pre-trial and main trial phases.

A sign-off/sign-in process is included in the COLOR III trial in order to evaluate each centre's capability to (i) recruit and randomise patients, (ii) comply with the treatment protocol and (iii) collect required data. Centres that wish to participate in COLOR III trial will be required to recruit and randomise 5 patients following the study protocol. A pre-trial checklist will be used to measure the compliance.

If a centre is unsuccessful in completing the Trial Quality Assurance Procedure, the evidence will be reviewed by the COLOR III steering committee and more evidence will be required for the component that is unsatisfactory. Within the scope of Surgical Quality Assurance, surgeons will be required to gain more experience with the support from COLOR III expert group and re-assessed.

The data collected during this Trial Quality Assurance Phase will not contribute to the main trial.

Before the trial entry, each surgeon will be required to submit 2 unedited videos for both laparoscopic and transanal TME. Two reviewers will assess the videos independently using the Competency Assessment Tool as the pre-trial entry procedure. During the main trial period, each surgeon will be required to submit 1 unedited video for every 3 cases for both laparoscopic and TaTME. The videos will be assessed using the Competency Assessment Tool to monitor the adherence to agreed standards.

Follow-up

Follow-up will be carried out (according to ESMO guidelines) yearly for a period of 5 years at the outpatient clinic (Fig. 1).[15] More frequent visits and additional examination will be performed on indication or to the preference of the attending surgeon. Three years post-operatively, an MRI of the pelvis will be performed to exclude local recurrence. A chest radiograph and a liver ultrasound or CT scan of thorax and abdomen will be done to assess any development of distant metastases. Recurrences and deaths should be reported to the coordinating centre through the COLOR III online platform or telephone within 2 weeks of detection. Follow-up of patients with recurrent disease will be continued until at least 3 years after detection or until death. Post-operative health-related quality of life (quality-adjusted life years) and functional outcome will be evaluated at 1, 3, 6, 12, 24 and 36 months post-operatively (measured with EORTC QLQ-CR29 and C30, EQ-5D and LARS questionnaires).

Endpoints

The primary endpoint of this trial is involvement of CRM. The CRM is deemed involved if malignant cells are found at microscopical assessment within 1 mm between the outermost part of the tumour and the CRM or between lymph nodes bearing tumour cells and the CRM. Secondary endpoints include completeness of mesorectum, residual mesorectum, morbidity and mortality, local recurrence, disease-free and overall survival, percentage of sphincter-saving procedures, functional outcome and quality of life.

Figure 1. Follow-up scheme

	1 month	3 months	6 months	9 months	12 months	18 months	24 months	36 months	48 months	60 months
Clinical evaluation		X	X	X	X	X	X	X	X	X
CEA		X	X	X	X	X	X	X	X	X
Colonoscopy					X				X	
CT-thorax/abdomen or CXR and ultrasound liver			X		X	X	X	X	X	X
MRI-pelvis								X		
Functional outcome and HrQoL	X	X	X		X		X	X		

Statistical analysis

Involved CRM in laparoscopic TME for mid and low rectal carcinomas is estimated to be 7%. The primary objective of the trial is to demonstrate a reduction in 4% of involved CRM after TaTME compared to laparoscopic TME. To demonstrate a difference of 4% (7-3%) at a randomisation ratio of 2:1, 732 TaTME patients and 366 laparoscopic TME patients are required for inclusion to generate a power of 80% for this trial. Baseline numerical data will be described in means, standard deviations or medians and interquartile ranges; baseline categorical data will be displayed in percentages. All comparative analyses will be conducted on an 'intention to treat' basis. Consequently, patients who are randomised to TaTME and converted to a laparoscopic or open TME will be analysed in the TaTME group. Patients who are randomised to a laparoscopic resection and converted to TaTME or open TME will be analysed in the laparoscopic group. Ninety days post-operative mortality, pathological resection margin and complication rates will be compared using the Chi-square test or an exact test if necessary. Local recurrence rate, disease-free and overall survival will be compared using the log-rank test. Exploratory analysis of the prognostic effects of various baseline factors on disease-free survival will be carried out through multivariate Cox regression. Apart from intention to treat analyses, per protocol analyses will be applied.

Accrual and limitations

For inclusion of 1098 patients, approximately 4 years are needed. Because at the start of the trial accrual will be limited to the main centres, the estimated accrual per year will be as follows:

Year 1: 108 patients (5 hospitals, approximately 2 patients per month)
Year 2: 290 patients (15 hospitals, approximately 1-2 patients per month)
Year 3: 300 patients (25 hospitals, approximately 1-2 patients per month)
Year 4: 400 patients (30 hospitals, approximately 1-2 patients per month)
Centralising MRI review will not be limitation of this study, because MRIs will be uploaded through an online tool and can be reviewed the same day.

Monitoring, audit and inspection

Governors will be appointed to monitor trial progress on site, as frequently as seen necessary. The medical ethical review board of the coordinating centre (VU University Medical Centre) will register the trial at the Clinical Research Bureau (CRB). The CRB will assign a data safety monitoring board (DSMB) to the trial. Interim analysis will not be performed, because the classification of this trial is not high risk. The DSMB will review the collected data and results.

Trial registration

The trial will be registered at http://clinicaltrials.gov.

Discussion

Worldwide, colorectal cancer is the third most common malignancy in males after prostate and lung cancer and the second most common malignancy in females after breast cancer. Each year, colorectal cancer afflicts approximately 737,000 new patients and causes about 333,000 deaths in developed countries.[1] For curative therapy, surgical intervention is required.
Rectal cancer surgery is generally considered technically more challenging than colon surgery, mainly because of the limited workspace in the small pelvis. In particular, in mid and low rectal tumours it is more difficult to achieve a radical resection because of this limited workspace and moreover due to limited visualisation. In addition, patients are confronted with high morbidity rates due to poor anastomotic techniques and conversion. Furthermore, mid and low rectal cancer surgery is associated with higher rates of permanent colostomies compared with surgery for high rectal cancer.

A quality indicator for rectal cancer surgery is the CRM. An involved CRM of 2 mm or <2 mm is associated with a local recurrence risk of 16% compared with 5.8% in patients without involvement of CRM ($p < 0.0001$).[16] Various large randomised controlled trials reported an involved CRM in 7.7-16% of patients operated because rectal cancer and higher rates of involved CRM were reported in distal rectal tumours compared to mid and proximal rectal tumours.[4,16-18]

To overcome the lack of visibility in the small pelvis and theoretically improve the rate of radical resections and decrease the rate of involved CRMs, Lacy et al.[9] introduced a transanal approach for TME in 2010. The TaTME has been developed with use of laparoscopic single port platforms to improve the quality of the TME procedure in mid and low rectal cancer. In TaTME, the tumour is distally approached through the anus with laparoscopic instruments. This facilitates a high-quality dissection of the distal mesorectum with adequate visual determination of the distal resection margin. The excellent view potentially enables nerve-sparing and sphincter-saving rectal excision.

From 2010 to date, several cohort series have been published regarding hybrid endoscopic TaTME. These series suggest that TaTME is feasible and safe regarding short-term outcomes and delivers high-quality resection specimen in selected patients. The series that excluded T4 tumours have demonstrated a promising CRM involvement of 0-5.4%.[10-13] The largest series, including 140 patients, reported CRM involvement of 6.4%; however, T4 tumours were not excluded and all patients with involvement of CRM were correctly predicted by MRI. Short-term morbidity and oncological results were comparable to other laparoscopic TME series.

[14] A randomised controlled trial is required to evaluate the role of TaTME for rectal cancer and to assess oncological outcomes on the long term.

Before adaptation of TaTME as standard surgical therapy for mid and low rectal cancer, a well-designed study is essential to demonstrate its efficacy and safety in a multicentre randomised setting: COLOR III trial. The primary concern is oncological safety in terms of CRM involvement and local recurrence rate. Secondary concerns are safety in terms of morbidity and functional outcome. Furthermore, a major challenge in surgical cancer clinical trials is lack of consistency in surgical quality. This study aims at addressing this limitation by applying a robust surgical Quality Assurance Protocol prior to the start and throughout the clinical trial to ensure consistency and validity.

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CHAPTER 10

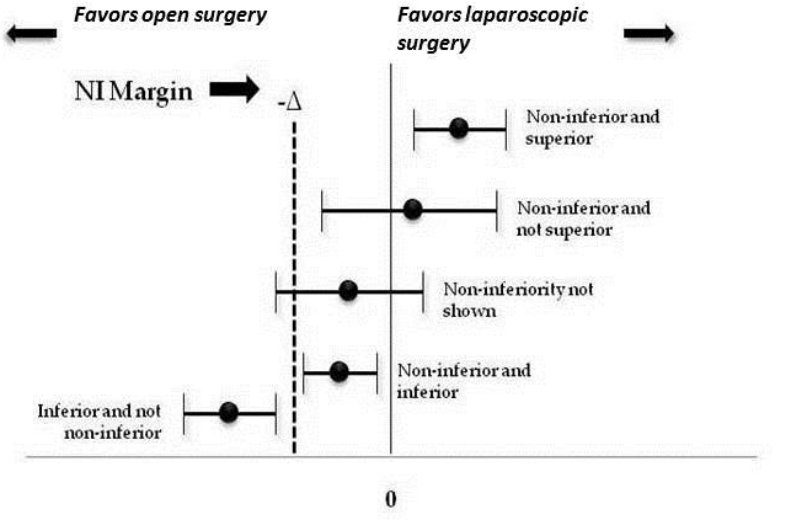
Discussion and future perspectives

Randomized clinical trials

The outcomes of laparoscopic surgery for colorectal cancer have been evaluated in many studies. After several large randomized clinical trials (RCTs) (CLASICC trial, COLOR trial, Barcelona trial)[1-3] showed that the laparoscopic approach was safe in patients with colon cancer, the next step was to investigate laparoscopic surgery for rectal cancer, considered technically more challenging. The COLOR II trial, including 1044 patients, was conducted with the aim to compare laparoscopic and open surgery in patients with rectal cancer. Short-term outcomes were similar to the outcomes in colon cancer patients.[4] At 3 years after surgery, the primary endpoint locoregional recurrence was 5% for both laparoscopic surgery and open surgery with a confidence interval (CI) for the difference of -2.6% to 2.6%.[5] The size of the cohort in our study allowed for the use of a noninferiority margin of 5%, whereas in the smaller COREAN trial (340 patients), the noninferiority margin was 15%. Primary endpoint of the COREAN trial was 3 year disease-free survival and was 72.5% for the open surgery group and 79.2% for the laparoscopic surgery group, with a CI around the difference of -15.8 to 2.4.[6]

On the contrary, recently two other large randomized trials - the ACOSOG Z6051 trial from the US and ALaCaRT trial from Australia - comparing laparoscopic and open resection of rectal cancer questioned the safety of laparoscopic surgery, because both trials could not establish noninferiority of the laparoscopic approach in terms of adequate surgical resection.[7,8] Only the ACOSOG Z6051 trial gave as explanation for the outcome of the study that proctectomy is challenging at baseline and that the available laparoscopic instruments hamper adequate complex maneuvers deep in the narrow pelvis. However, the COREAN and COLOR II trial encountered the same problem regarding use of rigid in-line laparoscopic instruments and these trials did observe noninferiority for laparoscopic rectal cancer resection compared to open resection.

It is often assumed that RCTs have high level of evidence. However, several aspects have to be taken into account. RCTs with less than 80% of follow-up are considered the same level of evidence as individual cohort studies.[9] The same applies to RCTs with a wide confidence interval. The confidence interval represents the range around a study's result within which we would expect the true value to lie. It is even noted that such evidence is inconclusive, and therefore can only generate Grade D recommendations. Factors that can contribute to wider confidence intervals are a small number of patients and great variability in surgical technique. Another important factor when interpreting study results is the noninferiority margin, which represents the maximum extent of clinical noninferiority. This means when no significant difference is found, there can still be a true difference with a value smaller than the noninferiority margin.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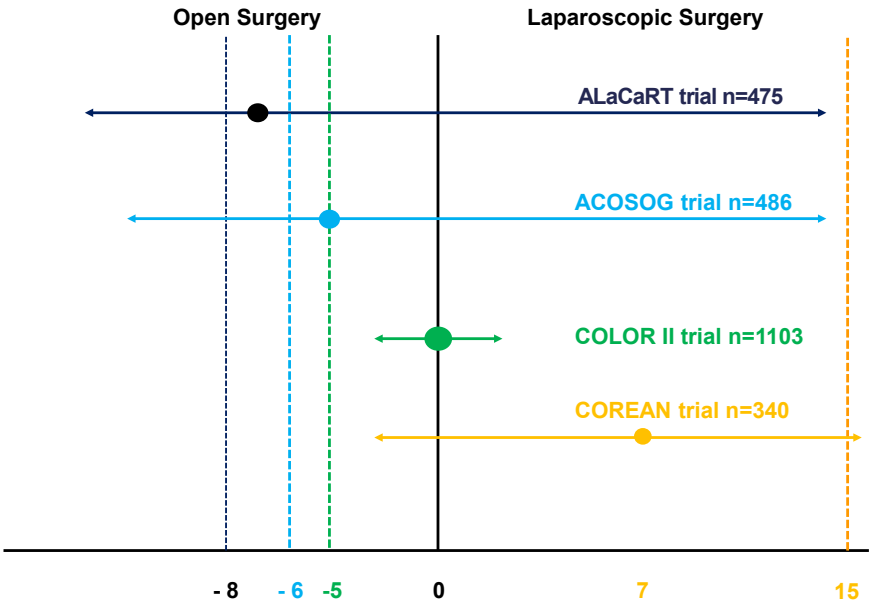
Open Surgery
Laparoscopic Surgery
ALaCaRT trial n=475
ACOSOG trial n=486
COLOR II trial n=1103
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The ACOSOG Z6051 and ALaCaRT trials both reported very wide confidence intervals around the difference of the primary endpoint (-12.4% to ∞ and -10.8% to ∞, respectively), which could indicate that the laparoscopic technique was not completely standardized. Another reason for the wide confidence intervals could be the use of a surrogate endpoint. Furthermore, the trials randomized 486 and 475 patients respectively, and these numbers could have been too small to reach noninferiority. Both trials acknowledge long-term clinical outcomes on recurrence and survival are needed. Confirming laparoscopic surgery for rectal cancer to be noninferior to open surgery should be based on the long-term results.

Lessons learned

The COLOR II trial is one of the largest randomized trials for rectal cancer. Because of the large number of patients, overall follow-up rate of 99% and the narrow confidence interval around the difference regarding the primary endpoint, the results can be considered as high quality evidence (level 1b). It has been over 13 years since the study was designed and a lot can be learned from its design. Because collecting data was performed through paper CRFs, we encountered some problems. It was sometimes difficult to read the results because some were handwritten and not reported through multiple options. Furthermore, not all requested information was always provided. Moreover, operative details were collected, but not every detail can be reported on paper. Therefore, when complications occurred or patients developed locoregional recurrence, a possible cause could not always be found. The complete surgical videos would have provided much more information. The primary endpoint was a pathological endpoint, however, another limitation was the absence of centralized evaluation of the resected specimens. Furthermore, use of different imaging methods was permitted to determine the location of the tumor. It would have been preferable to standardize the imaging technique of the pelvis and centrally review the tumor location by independent professionals.

One of the demerits of high quality randomized clinical trials accruing high numbers of patients is that the interval between commencement of the trial and reporting long-term outcomes lasts in most instances approximately a decade. Within that time frame, management protocols in health care frequently change and are implemented in the care of those patients involved in the clinical trial rendering interpretation of some outcomes more complex. International collaboration is mandatory to reduce completion time of large randomized trials.

Furthermore, a major challenge in surgical cancer clinical trials is lack of consistency in surgical quality. The international multicenter COLOR III trial was meticulously designed with the aim to compare TaTME to laparoscopic TME in patients with mid and low rectal cancer. The study

aims at addressing the limitation of lack in surgical quality by applying a robust surgical quality assurance protocol prior to the start and throughout the clinical trial to ensure consistency and validity. The trial is therefore unique in its design and extensive quality assurance. All data will be collected digitally and when entering the data one can only continue when all requested data on a certain page is provided. All surgical videos will be uploaded and when complications occur or patients develop locoregional recurrence, the videos could provide information on the cause.

Future perspectives of rectal cancer treatment

Current treatment strategies for rectal cancer focus on tailored neoadjuvant treatment with radiotherapy or combined chemoradiation to decrease the risk of recurrence and to downstage the cancer. The main cornerstone remains radical surgical treatment. With current strategies adequate local control is achieved, although at the cost of morbidity and functional impairments. Research is mainly focused on prevention, early detection and organ preserving therapies. Since rectal cancer surgery is associated with significant morbidity and decrease in quality of life, different treatment strategies to preserve function and quality of life without hampering oncological outcome are being evaluated. Three developments have increased the interest in rectal preserving treatment. On the one hand screening programs have resulted in a shift towards more early staged rectal cancer which potentially can be treated locally. On the other hand multidisciplinary neoadjuvant treatment enables downstaging of the primary tumor which could then potentially also be treated locally. At last, neoadjuvant treatment could result in complete remission of the tumor and local excision could be avoided.

The TESAR trial, opened in the beginning of 2016 and compares radical surgery versus adjuvant chemoradiotherapy after local excision for early rectal cancer.[10] The expectation is that local excision followed by chemoradiotherapy will result in similar oncological outcome and is associated with less morbidity and better function and quality of life compared to local excision followed by conventional radical surgery. However, radiotherapy potentially adds morbidity by radiation of a relative large field. New techniques allow precise measurement before and during radiation limiting collateral damage. With the TESAR trial a small field limited to the mesorectum is being evaluated. The recently started STARTREC trial investigates rectal preserving treatment therapies by neoadjuvant therapy followed by radical surgery or rectal preserving strategies.[11] The rectal preserving group consists of two arms: one arm will receive short-course 5x5Gy radiotherapy, the other arm will receive chemoradiotherapy with capecitabine and concurrent long-course radiotherapy. Depending on the response of the tumor to the neoadjuvant treatment patients will subsequently undergo LAR (in case of no

response), TEM (in case of partial response) or 'wait and see' policy with intensive follow-up (after complete response). A nonoperative 'wait and see' approach in case of complete clinical response after neoadjuvant therapy for rectal cancer is main focus in other studies as well. The functional advantage of these alternative is clear, but there is concern about the oncological risk. Although the available studies suggest that with adequate selection and follow-up this risk is small, the evidence is still weak. Because of patients' high interest in preserving quality of life, clinicians should cautiously move ahead and offer the option of organ preservation to patients in a controlled setting while awaiting further evidence.[12-16]

In most rectal cancer trials focusing on minimizing the surgical trauma, T4 tumors were excluded, thus the results cannot be extrapolated to these type of tumors. Therefore, there still is a role for open rectal cancer surgery in patients with large and invasive tumors. Furthermore, it is unlikely that in this century surgery will lose its role in the multimodality treatment in patients with rectal cancer. The trials investigating a wait and see policy include early rectal cancers and are not suitable for larger bulky tumors. For locally advanced rectal cancers the gold standard of curative treatment still is surgical resection. In patients not suitable for organ preservation treatment, TaTME could become the standard treatment instead of LAR in case of mid and low rectal tumors. However, first the COLOR III trial should provide evidence for the TaTME to result in similar recurrence and survival rates as laparoscopic resection alone.

Future developments in surgery

Robotic-assisted laparoscopic surgery has become more popular in rectal cancer surgery. However, there has been significant debate about the potential oncologic benefit of the use of robotic surgery in the treatment of patients with rectal cancer. One of the largest randomized trials investigating the technique is the RObotic versus LAparoscopic Resection for Rectal cancer (ROLARR) trial. The ROLARR trial was conducted in 29 hospitals in 10 countries and 471 patients were randomized to laparoscopic (234) or robotic (237) TME for rectal cancer.[17] The results have not been published yet but were presented and similar outcomes in the two treatment groups were observed regarding quality of TME, involvement of CRM and 30-day morbidity. However, robotic surgery also has its downsides. Besides the size of the available systems and high costs, lack of tactile feedback is an essential limiting factor.[18] One of the benefits of robotic surgery is the 3D view of the surgical field. However, nowadays 3D is also available for laparoscopic surgery and with the introduction of 4K technology, which allows surgeons to observe fine patterns and structures in high precision, the role of robotic surgery in rectal cancer remains under debate.

Furthermore, new developments in smaller and more precise instruments will certainly have a place in rectal cancer surgery in the future. Moreover, virtual reality has been introduced and will have its impact in the operating room. Potentially technical performance will be improved as an optimal enlarged view of the surgical field might be achieved combined with real life input from imaging technology such as MRI and CT and/or enhanced visualization of nerves and blood vessels.[19-21] The role of these techniques is still being evaluated and of course introduction on a larger scale should be accompanied by an extensive quality assurance program.

Future developments in diagnostics and therapy; towards precise tailoring of therapy

Diagnosis of tumors requiring adjuvant therapy or tumors that can be treated locally and might require adjuvant therapy is a major challenge. With low sensitivity rates of MRI and the serum CEA tumor marker, exact tailoring of the appropriate therapy would still be the ultimate goal. An exciting new technology which detects tumor derived mutated DNA fragments in patients with primary rectal cancer in peripheral blood, could potentially select those patients that need radical surgery or patients that need local surgery.[22-24] In addition, the patients in need for adjuvant therapy after local excision could be identified with these liquid biopsies. Further knowledge of the driver DNA mutations within the primary tumor could direct future targeted therapy. Surgical excision of the (rest) tumor will remain the main stay of treatment but in a restrictive and tailored way with focus to both oncological outcome and quality of life.

As result of all the extensive research to develop less invasive but oncologically safe therapies for patients with rectal cancer, it is expected that in the future patients with rectal cancer will experience less morbidity and at least similar recurrence and survival outcomes compared with patients that are treated for rectal cancer in this period of time.

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Summary

Summary

Chapter 1 consists of the introduction of this thesis. Colorectal cancer is the third most common cancer worldwide and accounts for nearly 1.4 million new cases and 694,000 deaths per year. Approximately one third of all colorectal cancers are localized in the rectum. Treatment of patients with rectal cancer has evolved significantly during the past two centuries resulting in improved prognosis and reduced morbidity rates. However, new surgical techniques are still being developed to further improve short- and long-term outcomes in patients with rectal cancer. In 2010 the transanal approach (TaTME) was introduced by the group of Lacy. The TaTME has high potential, however extensive evaluation in a well-designed multicenter randomized trial is needed to come to unequivocal conclusions.

Chapter 2 provides a historical overview of rectal cancer treatment and introduces the COLOR II trial that compared laparoscopic and open surgery in a randomized setting. Laparoscopic rectal cancer surgery has gained popularity over the past decade, however there is potential for improvement regarding incomplete resections, morbidity, and sphincter-saving procedures. In 2009 the transanal TME was introduced giving better visualization and facilitating mobilization of the distal rectum. The COLOR III trial will be conducted to evaluate outcomes of this new technique.

In **Chapter 3**, 10-year follow-up results of the Dutch patients of the first COLOR trial are reported. In this trial laparoscopic and open surgery for colon cancer were compared. In total 1248 patients were included of which 329 were Dutch. At 10 years after either laparoscopic or open surgery disease-free and overall survival rates, as well as recurrence rates were similar in both treatment groups.

Chapter 4 represents the primary endpoint of the COLOR II trial, locoregional recurrence at 3 years after either laparoscopic or open resection of nonmetastatic and noninvasive rectal cancer. In total 1044 were included, 699 in the laparoscopic-surgery group and 345 in the open-surgery group. In both groups the locoregional recurrence rate was 5%. Main secondary outcomes, disease-free and overall survival, were similar in both groups as well. In patients with stage III rectal cancer improved disease-free survival was found in patients that underwent laparoscopic surgery compared to patients that underwent open surgery.

Chapter 5 consists of the 5-year follow-up results of the COLOR II trial. Similar to the results at 3 years follow-up, locoregional recurrence rates were comparable in both groups. Regarding

disease-free and overall survival, similar rates in the laparoscopic and open group were found as well. The better disease-free survival after laparoscopic resection in patients with stage III disease remained present at 5 years follow-up.

In **Chapter 6** a subanalysis of the COLOR II trial was performed and risk factors for conversion were evaluated. Of 697 laparoscopically operated patients, 114 patients were converted to open surgery (16%). In male patients 18% of the operations were converted versus 13% in female patients (difference not significant). Conversion rates at the start and at the end of the trial were comparable. Analysis of risk factors for conversion showed that height of the tumor >5cm, BMI >25 and age >65 years were all associated with a higher risk of conversion. Previous abdominal surgery, gender, ASA-classification, previous chemoradiotherapy and cT-stage turned out to be no predictive factors for conversion. Because the greater part of patients with a tumor located within 5cm from the anal verge underwent an APR, extra analyses were performed including only patients who underwent a sphincter saving procedure. In this group of patients risk factors for conversion were BMI >25 and age >65 years.

Chapter 7 consists of the first results of the TaTME technique in two Dutch hospitals. In total 80 patients were operated between June 2012 and May 2014. In four patients the surgery had to be converted (5%). Median operative time was 204min (range 91-447). The postoperative morbidity rate was 39%. In ten cases (12%) the complications were graded as severe (Clavien-Dindo grade 3, 4 and 5). Median hospital stay was eight days (range 3-41). In 88% of the patients the specimen was judged complete. Involvement of CRM was reported in two patients (2.5%).

Chapter 8 presents the results of a systematic literature review on TaTME for rectal cancer. The aim of the review was to provide data on the safety of TaTME. A total number of 33 studies were identified, including 794 patients. Of all variables a weighted mean was calculated based on the number of included patients per study. To evaluate a potential learning curve effect, low volume centres (n≤30 total volume) were compared with high volume centres (n>30 total volume). The major complication rate was 11.5%. Major complication rates were 10.5% vs 12.2% in high vs low volume centres. The CRM was involved in 4.7% and was 4.8% vs 4.5% in low vs high volume centres. The quality of the mesorectum was “complete” in 87.6%. In high vs low volume centres TME quality was “complete” in 89.7% vs 80.5%. In the total group distal resection margins were involved in 0.2% of the patients and in high vs low volume centres in 0.3% vs 0.4%. Overall high volume centres had better outcome compared to low volume centres.

Chapter 9 is formed by the study protocol of the COLOR III trial, a randomized controlled trial to compare TaTME and laparoscopic TME in patients with mid and low rectal cancer. Primary endpoint of this trial is the involvement of CRM. In laparoscopic TME the percentage of involved CRM is estimated 7%. To detect a reduction to 3% a total of 1098 patients is needed, 732 patients in the TaTME arm and 366 patients in the laparoscopic TME arm. It will be stratified for T-stage, preoperative radiotherapy, height of the tumour (mid or low), gender and BMI. Secondary endpoints include completeness of mesorectum, residual mesorectum, morbidity and mortality, local recurrence, disease-free and overall survival, sphincter-saving procedure rate, functional outcome and quality of life. A Quality Assurance Protocol including centralised MRI review, histopathology re-evaluation, standardisation of surgical techniques, and monitoring and assessment of surgical quality will be conducted. The hypothesis is that TaTME will result in a better mesorectum specimen quality with a lower rate of involved CRM and therefore lower rate of local recurrence.

Chapter 10 comprises the discussion of this thesis and future perspectives of rectal cancer treatment.

Samenvatting

Samenvatting

Hoofdstuk 1 vormt de introductie van dit proefschrift. Het colorectaal carcinoom is de op twee na meest voorkomende vorm van kanker wereldwijd en leidt jaarlijks tot bijna 1.4 miljoen nieuwe gevallen en 694.000 doden. Ongeveer een derde van alle colorectaal carcinomen bevindt zich in het rectum. De behandeling van patiënten met rectumcarcinoom is de afgelopen twee eeuwen enorm verbeterd met als resultaat een betere prognose en verminderde morbiditeit. Toch worden nog altijd nieuwe chirurgische technieken ontwikkeld om de korte en lange termijn uitkomsten van patiënten met rectumcarcinoom verder te verbeteren. In 2010 heeft de groep van Lacy de transanale benadering geïntroduceerd (TaTME). De TaTME heeft veel potentie, maar zal eerst grondig geëvalueerd moeten worden in een goed opgezette multicenter gerandomiseerde studie om tot definitieve conclusies te komen.

Hoofdstuk 2 biedt een overzicht van de geschiedenis van de behandeling van het rectumcarcinoom en introduceert de COLOR II studie, waarin de laparoscopische en open operatie zijn vergeleken. De laparoscopische operatie is in de afgelopen tien jaar steeds populairder geworden, maar er is nog ruimte voor verbetering wat betreft incomplete resecties, morbiditeit en het aantal sfincter-sparende procedures. In 2010 is de transanale TME geïntroduceerd, waarbij beter zicht wordt verkregen en de mobilisatie van het distale rectum wordt vergemakkelijkt. De COLOR III studie zal worden verricht om de resultaten van deze nieuwe techniek te onderzoeken.

In **Hoofdstuk 3** worden de 10-jaars resultaten van de Nederlandse patiënten van de eerste COLOR studie gerapporteerd. In dit onderzoek werden de laparoscopische en open operatie voor het coloncarcinoom vergeleken. Er werden 1248 patiënten geïncludeerd, waarvan er 329 Nederlands waren. Na 10 jaar waren de ziektevrije en algehele overleving en recidief percentages gelijk in zowel de laparoscopische als de open operatie groep.

Hoofdstuk 4 beschrijft het primaire eindpunt van de COLOR II studie, het lokaal recidief 3 jaar na laparoscopische of open resectie van niet-gemetastaseerd en niet-invasief rectumcarcinoom. Er werden 1044 patiënten geïncludeerd, 699 in de laparoscopische operatie groep en 345 in de open operatie groep. In beide groepen had 5% van de patiënten een lokaal recidief na 3 jaar. De belangrijkste secundaire eindpunten waren ziektevrije en algehele overleving en waren ook gelijk in beide groepen. Patiënten met stadium III rectumcarcinoom hadden na een laparoscopische operatie een hogere ziektevrije overleving dan patiënten na een open operatie.

Hoofdstuk 5 beschrijft de resultaten van de COLOR II studie 5 jaar na de operatie. Het lokaal recidief percentage was net als 3 jaar na de operatie gelijk in beide groepen. Ook de ziektevrije en algehele overleving en het percentage recidieven waren gelijk. De hogere ziektevrije overleving bij stadium III ziekte na laparoscopie werd ook nog 5 jaar na de operatie waargenomen.

Hoofdstuk 6 bestaat uit een subanalyse van de COLOR II studie, waarin risicofactoren voor conversie werden onderzocht. Van de 697 patiënten die laparoscopisch werden geopereerd, waren er 114 geconverteerd naar een open procedure (16%). Van de mannelijke patiënten werd 18% geconverteerd en van de vrouwelijke patiënten 13% (verschil niet significant). Het percentage conversies aan het begin en aan het einde van de studieperiode waren vergelijkbaar. De analyse van risicofactoren voor conversie toonde dat locatie van de tumor >5cm, BMI >25 en leeftijd >65 jaar waren geassocieerd met een hogere kans op conversie. Eerdere abdominale operaties, geslacht, ASA-klasse, eerdere chemoradiotherapie en cT-stadium waren geen voorspellende factoren voor het optreden van conversie. Omdat bij het merendeel van de patiënten met een tumor binnen 5cm van de anus een APR was verricht, werd een aanvullende analyse gedaan waarbij alleen patiënten werden geïncludeerd die een sfincter-sparende operatie hadden ondergaan. In deze groep patiënten waren BMI >25 en leeftijd >65 jaar risicofactoren voor conversie.

Hoofdstuk 7 bestaat uit de eerste resultaten van de TaTME procedure in twee Nederlandse ziekenhuizen. In totaal werden 80 patiënten geopereerd tussen juni 2012 en mei 2014. In vier patiënten werd de procedure geconverteerd naar een open procedure (5%). De mediane operatieduur was 204min (range 91-447). De postoperatieve morbiditeit bedroeg 39%. In tien gevallen (12%) traden ernstige complicaties op (Clavien–Dindo graad 3, 4 en 5). De mediane ziekenhuisopname was acht dagen (range 3-41). In 88% van de patiënten werd het preparaat beoordeeld als “compleet”, betrokkenheid van de CRM werd gevonden in twee patiënten (2.5%).

Hoofdstuk 8 beschrijft de resultaten van een systematisch literatuuronderzoek naar TaTME voor rectumcarcinoom. Het doel van dit onderzoek was inzicht te verkrijgen in de veiligheid van de TaTME procedure. In totaal werden 33 studies geïdentificeerd, met in totaal 794 patiënten. Van alle variabelen werd een gewogen gemiddelde berekend op basis van het aantal geïncludeerde patiënten. Om een mogelijk leercurve effect te evalueren, werden centra met een laag volume (n≤30 totaal volume) vergeleken met centra met een hoog volume (n>30 totaal volume). Het percentage ernstige complicaties in de hele groep was 11.5%. Voor hoog vs laag volume centra was dit 10.5% vs 12.2%. De CRM was betrokken in 4.7% en was 4.5%

vs 4.8% in hoog vs laag volume centra. Het mesorectum was “compleet” in 87.6%. In hoog vs laag volume centra was het mesorectum “compleet” in 89.7% vs 80.5%. In de totale groep had 0.2% van de patiënten betrokkenheid van de distale resectiemarge. In hoog vs laag volume centra was dit 0.3% vs 0.4%. Over het algeheel hadden hoog volume centra betere uitkomsten dan laag volume centra.

Hoofdstuk 9 wordt gevormd door het studieprotocol van de COLOR III studie, een gerandomiseerde studie waarin de TaTME en laparoscopische TME worden vergeleken in patiënten met mid en laag rectumcarcinoom. Het primaire eindpunt van deze studie is de betrokkenheid van de CRM. Voor de laparoscopische TME wordt het percentage betrokkenheid van de CRM geschat op 7%. Er zijn 1098 patiënten nodig om een afname naar 3% te vinden, 732 patiënten in de TaTME groep en 366 patiënten in de laparoscopische TME groep. Randomisatie zal worden gestratificeerd voor T-stadium, preoperatieve radiotherapie, locatie van de tumor, (mid of laag), geslacht en BMI. Secundaire eindpunten zijn compleetheid van het mesorectum, resterend mesorectum, morbiditeit en mortaliteit, lokaal recidief, ziektevrije en algehele overleving, aantal sfincter-sparende procedures, functionele uitkomsten en kwaliteit van leven. Er zal een Kwaliteitsborging Protocol worden nageleefd, dat bestaat uit gecentraliseerde MRI beoordeling, histopathologische herbeoordeling, standaardisatie van chirurgische techniek en het monitoren en beoordelen van de kwaliteit van de chirurgie. De hypothese is dat TaTME zal leiden tot een betere kwaliteit van het mesorectum met een lager percentage betrokkenheid van de CRM en daardoor een lager lokaal recidief percentage.

Hoofdstuk 10 omvat de discussie van dit proefschrift en de toekomstperspectieven van de behandeling van het rectumcarcinoom.

List of publications

List of publications

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Curriculum vitae

Curriculum vitae

Charlotte Leonore Deijen werd geboren in Amsterdam op 6 augustus 1985. Als middelste van drie kinderen groeide zij op in Bussum. In 2003 behaalde zij haar gymnasiumdiploma aan het Sint Vituscollege in Bussum en aansluitend startte zij met de opleiding Geneeskunde aan de Vrije Universiteit in Amsterdam. Tijdens de studie en met name tijdens de coschappen ontstond haar interesse voor de chirurgie en na een oudste coschap chirurgie in het Medisch Centrum Alkmaar heeft zij daar met veel plezier als arts-assistent niet in opleiding gewerkt. Tijdens deze periode werd haar duidelijk dat zij grote affiniteit had met de oncologische zorg. Vanuit daar kreeg zij de mogelijkheid te starten met een promotietraject onder prof. dr. H.J. Bonjer in het VU medisch centrum in Amsterdam en heeft zij zich drie jaar fulltime gericht op onderzoek naar de chirurgische behandeling van het colorectaal carcinoom. Een jaar voor het einde van dit traject werd haar interesse voor de radiotherapie gewekt en is zij in oktober 2016 direct aansluitend aan haar promotietraject gestart met de opleiding tot Radiotherapeut-oncoloog in het Antoni van Leeuwenhoekziekenhuis in Amsterdam.

Dankwoord

Dankwoord

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